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Executive Summary: Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists.

Insights from the Society of Infectious Diseases Pharmacists

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Vancomycin is one of the most commonly prescribed antibiotics and has been a mainstay of therapy for patients with suspected or documented antibiotic-resistant gram-positive infections for decades. Despite its frequent use, optimal and safest dosing remains controversial. In 2009, consensus guidelines were developed to facilitate vancomycin dosing and monitoring. For serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections, the 2009 consensus guidelines indicated that the primary pharmacokinetic/pharmacodynamic

(PK/PD) target for vancomycin is an area-under-the-concentration-time curve to minimum inhibitory concentration ratio (AUC/MIC) ≥400. As AUCs are not routinely determined in clinical practice, the 2009 consensus guidelines recommended trough monitoring and maintaining trough concentrations between 15-20 mg/L as a surrogate marker of the AUC/MIC (target 400 mg*h/L) for ease of managing therapy and simplifying dose adjustments and monitoring.

With widespread adoption of these recommendations into clinical practice, there have been numerous reports of increased nephrotoxicity, consistently in both adults and children, associated with maintaining vancomycin troughs between 15-20 mg/L without any notable improvement in outcomes. Studies indicated that there is a high degree of inter-individual variability between a measured trough concentration and the actual daily AUC value. A trough value of 15-20 mg/L will almost always ensure a daily AUC in excess of 400 mg*L/h. However, there is considerable variability in the upper range of AUC values and most patients will have a daily AUC in excess of 600 mg*L/h. Patients with daily AUCs in excess of 600 mg*L/h were reported to be at an increased risk of vancomycin-associated nephrotoxicity across a number of studies. Furthermore, several studies indicate that AUC-guided dosing relative to trough-based monitoring is associated with less nephrotoxicity and comparable outcomes.

This Vancomycin Consensus Guideline for dosing and monitoring vancomycin is an updated revision to the 2009 guidelines and was developed by the American Society of Health-Systems Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists vancomycin guidelines committee. Based on best available evidence, these guidelines conclude that AUC-guided dosing and monitoring is the most accurate and safest way to optimize vancomycin dosing. For AUC-guided dosing, the vancomycin minimum inhibitory concentration by broth microdilution (MIC_{BMD}) should be assumed to be 1 mg/L since the vancomycin MIC_{BMD} for MRSA is 1 mg/L or less at most institutions and measurement of MIC values is imprecise with a range of accuracy of ± 1 log2 dilutions. There is a high degree of variability between commercially available MIC testing methods relative to the MIC_{BMD} method (see MIC Susceptibility Testing section of full guidelines). Given this variability between MIC values and testing methods routinely performed

at most institutions, it further supports the use of AUC (assuming a MIC_{BMD} of 1 mg/L) to guide vancomycin empiric dosing.

In both adults and pediatrics, daily AUCs should be maintained between 400 and 600 mg*hr/L to achieve clinical efficacy while improving patient safety for patients with suspected or definitive serious invasive MRSA infections. Given the importance of early, appropriate therapy, targeted AUC exposures should be achieved early during the course of therapy, preferably within the first 24 to 48 hours. Use of loading doses (20-35 mg/kg based on actual body weight) should be considered in patients who are critically-ill or in the intensive care unit, requiring renal replacement therapy, or receiving continuous infusion therapy of vancomycin. Since the estimated volume of distribution for vancomycin does not increase in a proportionate manner with actual body weight, a vancomycin loading dose of 20-25 mg/kg using actual body weight with a maximum of 3000 mg may be considered in obese adult patients with serious infections.

While AUC monitoring was perceived to be a cumbersome and intensive process in the past, it is possible to accurately estimate the AUC with limited PK sampling. One such approach involves the use of Bayesian software programs to estimate the vancomycin AUC value with minimal PK sampling (i.e., one or two vancomycin concentrations) and provide AUC-guided dosing recommendations in real-time. An alternative approach involves use of two concentrations (peak and trough) and simple analytic PK equations to estimate AUC values. The committee still endorses administering vancomycin as conventional intermittent doses but recognized that continuous infusion may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved.

Specific details for each section of the document, including references, can be found in the primary publication.[1] Recommendations for dosing in patients with obesity, patients on renal replacement therapy, and pediatrics are provided in this consensus guideline update. It is important to recognize that almost all the data available on vancomycin PK/PD and toxicodynamics have been derived from patients who have been treated for serious MRSA infections. Extreme caution should be applied and extrapolating this information to mild non-

invasive infections or other bacterial species susceptible to vancomycin. The recommendations in this document should not circumvent sound clinical judgement in managing patients who require vancomycin therapy.

Table 1. Grading System for Recommendations Based on Quality of Evidence

Category and Grade	**Definition**
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert

	committees

Adapted from the Canadian Task Force on the Periodic Health Examination[2]

Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring

A. ADULTS AND PEDIATRICS
1. In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety **(A-II)**.
2. When transitioning to AUC/MIC monitoring, clinicians should conservatively target AUCs for patients with suspected or documented serious infections due to MRSA assuming a vancomycin MIC_{BMD} of 1 mg/L or less at most institutions. Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours **(A-II)**. As such, the use of Bayesian-derived AUC monitoring may be prudent in these cases since it doesn't require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.
3. Trough only monitoring, with target between 15–20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA **(A-II).** There is insufficient evidence to provide recommendations on whether trough only or AUC-guided vancomycin monitoring should be used among patients with non-invasive MRSA or other infections.
4. Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve sustained targeted AUC (assuming a MIC_{BMD} of 1 mg/L, unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk of nephrotoxicity (e.g., critically-ill patients

receiving concurrent nephrotoxins), patients with unstable (i.e., deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than three to five days). We suggest the frequency of monitoring be based on clinical judgement; frequent or daily monitoring may be prudent for hemodynamically unstable patients (e.g., end stage renal disease) and once-weekly monitoring for hemodynamically stable patients **(B-II)**.
5. Based on current national vancomycin susceptibility surveillance data, under most circumstances for empiric dosing, the vancomycin MIC should be assumed to be 1 mg/L. When the MIC_{BMD} is > 1 mg/L, the probability of achieving an AUC/MIC ≥ 400 target is unlikely with conventional dosing; higher doses may risk unnecessary toxicity and the decision to change therapy should be based on clinical judgement. In addition, when MIC_{BMD} < 1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on method used **(B-II)**.
6. The pharmacokinetics of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved **(B-II).**
7. Incompatibility with vancomycin and other drugs commonly co-administered in the ICU requires the use of independent lines or multiple-catheters when vancomycin is being considered for continuous infusion **(A-III)**.
B. ADULTS
8. Given the narrow vancomycin AUC range for therapeutic effect and minimal acute kidney injury (AKI), the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring **(A-II)**. We recommend to accomplish this in one of two ways. a. One approach relies on the collection of two concentrations (obtained near steady-state, post-distributional peak concentration at 1-2 hours after infusion and trough at end of dosing interval) preferably but not required during the same dosing interval (if possible) and utilizing first-order pharmacokinetic (PK) equations to estimate the AUC **(A-II)**.

b. The preferred approach to monitor AUC involves the use of Bayesian software programs, embedded with a PK model based on richly sampled vancomycin data as the Bayesian prior, to optimize the delivery of vancomycin based on the collection of one or two vancomycin concentrations, with at least one trough. It is preferred to obtain two PK samples (i.e., 1-2 hours post infusion and at end of dosing interval) to estimate the AUC with the Bayesian approach **(A-II)**. A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data are needed across different patient populations to confirm viability of using trough only data **(B-II)**.
9. Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8 to 12 hours as an intermittent infusion are recommended for most patients with normal renal function when assuming MIC_{BMD} of 1 mg/L **(A-II)**. In patients with normal renal function, these doses may not achieve therapeutic AUC/MIC target when the MIC is 2 mg/L.
10. *Continuous Infusion:* Based on current available data, a loading dose of 15-20mg/kg, followed by daily maintenance CI of 30-40mg/kg up to 60mg/kg, to achieve target steady-state concentration of 20-25mg/L may be considered for critically-ill patients **(B-II)**. AUC_{24} can be simply calculated when multiplying steady-state concentration (i.e., desired therapeutic range of 20-25 mg/L throughout entire dosing interval) by a factor of 24 **(B-II)**. Attaining the desired drug exposure may be more readily accomplished given the ease of sampling time and dosage adjustment by changing the rate of infusion which is a highly desirable feature in critically-ill patients **(B-II)**.
11. The risk of developing nephrotoxicity with continuous infusion appears to be similar or lower compared to intermittent dosing when targeting steady-state concentration 15-25 mg/L and trough 10-20 mg/L, respectively **(B-II)**. Definitive studies are needed to compare drug exposure based on measured AUC_{24} and factors that predispose to development of nephrotoxicity such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving continuous infusion vs. intermittent infusion of vancomycin.
12. In order to achieve rapid attainment of targeted concentrations in critically-ill patients with suspected or documented serious MRSA infections, a loading dose of 20-35 mg/kg can be

considered for intermittent administration of vancomycin **(B-II)**. Loading doses should be based on actual body weight and not exceed 3000 mg. More intensive and early therapeutic monitoring should also be performed in obese patients **(B-II)**.
13. *Adult Obesity:* A vancomycin loading dose of 20-25 mg/kg using actual body weight with a maximum of 3000 mg may be considered in obese adult patients with serious infections **(B-II)**. Empiric maintenance doses for most obese patients usually do not exceed 4500 mg/day, depending on their renal function **(B-II)**. Early and frequent monitoring of AUC exposure is recommended for dose adjustment, especially when empiric doses exceed 4000 mg/day **(A-II)**.
14. *Intermittent Hemodialysis:* Since efficacy data are unavailable for AUC < 400 mg*hr/L, monitoring based on pre-dialysis serum concentrations and extrapolating these values to estimate AUC is most practical. Maintaining pre-dialysis concentrations between 15 and 20 mg/L are likely to achieve the AUC of 400-600 mg*hr/L in the previous 24 hours **(C-III)**. Pre-dialysis serum concentration monitoring should be performed not less than weekly and should drive subsequent dosing rather than a strict weight-based recommendation, although these recommended doses provide a useful starting point until serum concentrations have been determined **(B-II).**
15. *Hybrid Dialysis Therapies (e.g. Slow-Low Efficiency Dialysis [SLED]):* Loading doses of 20-25 mg/kg actual body weight should be used, recognizing that these hybrid dialysis therapies efficiently remove vancomycin **(B-III)**. Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60-90 minutes of dialysis, as is done with standard hemodialysis **(B-III)**. Concentration monitoring should guide further maintenance doses**.**
16. *Continuous Renal Replacement Therapies (CRRT):* Loading doses of 20-25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20-25 mL/kg/hr **(B-II)**. Initial maintenance dosing for CRRT with effluent rates of 20-25 mL/kg/hr should be 7.5-10 mg/kg every 12 hours **(B-II)**. Maintenance dose and dosing interval should be based on serum concentration monitoring which should be conducted within the first 24 hours to ensure AUC/MIC targets are met. In fluid overloaded patients, doses may be

reduced as patients become euvolemic and drug Vd decreases. The use of continuous infusion vancomycin in patients receiving CRRT appears to be growing, and could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed **(B-II)**.
C. PEDIATRICS
17. Based on an AUC target of 400 mg*hr/L (but potentially up to 600 mg*hr/L assuming MIC of ≤ 1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60 to 80 mg/kg/day, divided every 6 to 8 hour, for children ages 3 months and older **(A-II)**.
18. The maximum empiric daily dose is usually 3600 mg/day in children with adequate renal function **(C-III)**. Most children generally should not require more than 3000 mg/day and doses should be adjusted based on observed concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2000 to 3000 mg/day **(A-III)**. Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal clearance as resolution of their renal function may occur within the first five days of therapy.
19. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for one trough concentration, or first-order PK equations with two concentrations **(B-II)**. The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring.

20. Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults **(B-III)**. Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy **(B-III)**.
21. Vancomycin exposure may be optimally maintained below the thresholds for AUC of 800 mg*hr/L and trough concentrations of 15 mg/L to minimize AKI **(B-II)**. The safety of vancomycin above 80 mg/kg/day has not been prospectively evaluated. Avoiding vancomycin doses ≥ 100 mg/kg/day is suggested since they are likely to surpass these thresholds **(B-III)**.
22. Insufficient data exist on which to base a recommendation for a loading dose among the non-obese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations from the neonate to adolescent **(C-III)**.
23. *Pediatric Obesity:* Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than normal weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to non-obese children, obese children < 12 years old, compared with those ≥ 12 years, may require higher mg/kg dose **(B-II)**.
24. *Pediatric Obesity:* Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and the risk of AKI. The specific recommendations for therapeutic monitoring in non-obese children may also apply for obese children **(B-II)**. A loading dose of 20 mg/kg by total body weight is recommended in obese children **(A-III)**.

25. *Neonates:* Doses recommended to achieve an AUC of 400 mg*hr/L (assuming an MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours, depending on post-menstrual age, weight and SCr **(A-II)**.

References

1. Rybak MJ, Le J, Lodise, TP, Levine, DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro B. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacist. *Am J Health-Syst.* 2019; publication pending
2. The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J. 1979;121(9):1193-254.

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Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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mg/L, the probability of achieving an AUC/MIC ≥ 400 target is unlikely with conventional dosing; higher doses may risk unnecessary toxicity and the decision to change therapy should be based on clinical judgement. In addition, when MIC_{BMD} < 1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on method used **(B-II)**.
6. The pharmacokinetics of continuous infusion suggest that such regimens may be a reasonable alternative to conventional intermittent infusion dosing when the AUC target cannot be achieved **(B-II).**
7. Incompatibility with vancomycin and other drugs commonly co-administered in the ICU requires the use of independent lines or multiple-catheters when vancomycin is being considered for continuous infusion **(A-III)**.
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9. Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8 to 12 hours as an intermittent infusion are recommended for most patients with normal renal function when assuming MIC_{BMD} of 1 mg/L **(A-II)**. In patients with normal renal function, these doses may not achieve therapeutic AUC/MIC target when the MIC is 2 mg/L.
10. *Continuous Infusion:* Based on current available data, a loading dose of 15-20mg/kg, followed by daily maintenance CI of 30-40mg/kg up to 60mg/kg, to achieve target steady-state concentration of 20-25mg/L may be considered for critically-ill patients **(B-II)**. AUC_{24} can be simply calculated when multiplying steady-state concentration (i.e., desired therapeutic range of 20-25 mg/L throughout entire dosing interval) by a factor of 24 **(B-II)**. Attaining the desired drug exposure may be more readily accomplished given the ease of sampling time and dosage adjustment by changing the rate of infusion which is a highly desirable feature in critically-ill patients **(B-II)**.
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15. *Hybrid Dialysis Therapies (e.g. Slow-Low Efficiency Dialysis [SLED]):* Loading doses of 20-25 mg/kg actual body weight should be used, recognizing that these hybrid dialysis therapies efficiently remove vancomycin **(B-III)**. Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60-90 minutes of dialysis, as is done with standard hemodialysis **(B-III)**. Concentration monitoring should guide further maintenance doses**.**

16. *Continuous Renal Replacement Therapies (CRRT):* Loading doses of 20-25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20-25 mL/kg/hr **(B-II)**. Initial maintenance dosing for CRRT with effluent rates of 20-25 mL/kg/hr should be 7.5-10 mg/kg every 12 hours **(B-II)**. Maintenance dose and dosing interval should be based on serum concentration monitoring which should be conducted within the first 24 hours to ensure AUC/MIC targets are met. In fluid overloaded patients, doses may be reduced as patients become euvolemic and drug Vd decreases. The use of continuous infusion vancomycin in patients receiving CRRT appears to be growing, and could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed **(B-II)**.

C. PEDIATRICS

17. Based on an AUC target of 400 mg*hr/L (but potentially up to 600 mg*hr/L assuming MIC of ≤ 1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60 to 80 mg/kg/day, divided every 6 to 8

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18. The maximum empiric daily dose is usually 3600 mg/day in children with adequate renal function **(C-III)**. Most children generally should not require more than 3000 mg/day and doses should be adjusted based on observed concentrations to achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2000 to 3000 mg/day **(A-III)**. Furthermore, close monitoring of observed concentrations and renal function is prudent in patients with poor or augmented renal clearance as resolution of their renal function may occur within the first five days of therapy.
19. AUC-guided therapeutic monitoring for vancomycin, preferably with Bayesian estimation, is suggested for all pediatric age groups, based on developmental changes of vancomycin CL documented from the newborn to the adolescent. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the application of Bayesian estimation for one trough concentration, or first-order PK equations with two concentrations **(B-II)**. The Bayesian AUC-guided dosing strategy may be an optimal approach to individualize vancomycin therapy in pediatrics since it can incorporate varying ages, weights, and renal function. Both serum concentrations of vancomycin and renal function should be monitored since vancomycin CL and creatinine CL are not always well correlated in pediatrics. Furthermore, aggressive dosing to maintain target AUC exposure and decrease the risk of potential AKI in treatment of MRSA infection necessitates drug monitoring.
20. Therapeutic monitoring may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections in children, as in adults **(B-III)**. Any delay in therapeutic monitoring should be based on severity of infection and clinical judgment. Dosing adjustment should be made for those with renal insufficiency, obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insufficiency, but subsequent adjustment (particularly within the first 5 days of therapy) may be necessary for those experiencing recovery of renal function. Sustained or subsequent decreases in dosage may be needed, particularly for those with chronic renal insufficiency and those receiving concurrent nephrotoxic drug therapy **(B-III)**.

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23. *Pediatric Obesity:* Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than normal weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to non-obese children, obese children < 12 years old, compared with those ≥ 12 years, may require higher mg/kg dose **(B-II)**.
24. *Pediatric Obesity:* Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and the risk of AKI. The specific recommendations for therapeutic monitoring in non-obese children may also apply for obese children **(B-II)**. A loading dose of 20 mg/kg by total body weight is recommended in obese children **(A-III)**.
25. *Neonates:* Doses recommended to achieve an AUC of 400 mg*hr/L (assuming an MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours, depending on post-menstrual age, weight and SCr **(A-II)**.