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Vancomycin Therapeutic Drug Monitoring for Serious Methicillin-Resistant *Staphylococcus aureus* Infections

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation Instrument
AGREE-REX	AGREE-Recommendation Excellence supplementary tool
AKI	acute kidney injury
ASHP	American Society of Health-System Pharmacists
AUC	area under the curve
CTFPHE	Canadian Task Force on the Periodic Health Examination
FCA	focused Critical Appraisal
IDSA	Infectious Diseases Society of America
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
PIDS	Pediatric Infectious Diseases Society
SIDP	Society of Infectious Diseases Pharmacists
VIN	vancomycin-induced nephropathy

Background

The diagnosis of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is determined when the causative *S. aureus* strain is found to be resistant to semi-synthetic penicillins such as methicillin or oxacillin.[1] Infections caused by MRSA represent a burden and an important public health issue worldwide and in Canada.[2-4] The mortality rates vary from 5% to 60%, depending on the affected population and the site of infection.[4]

Vancomycin is an intravenously administered glycopeptide antibiotic currently used to treat infections caused by gram-positive organisms and is considered a first-line therapy against MRSA and other resistant gram-positive infections.[1,5] In such situations, health professionals must rely on measuring optimal levels of vancomycin to guide treatment and adjust dosages, aiming to achieve a balance between maximizing efficacy and reducing toxicity, especially to avoid vancomycin-induced acute kidney injury (AKI).[5]

The predictor of vancomycin activity against MRSA is the 24-hour area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio — or AUC/MIC. The efficacy of vancomycin depends primarily upon the time its concentration exceeds the organism's MIC, with a commonly set target of an AUC/MIC ratio of ≥ 400.[6] However, reaching this goal with the AUC/MIC-based monitoring method is hampered by the need for complex calculations and multiple blood sampling.[7] A more pragmatic method commonly used for therapeutic monitoring in clinical practice is the measurement of trough levels of vancomycin, which requires one blood sample and serves as a surrogate marker for the target AUC/MIC over 24 hours.[1,7]

In 2009, a consensus guideline of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP)[8] endorsed the use of trough levels of vancomycin as the preferred therapeutic monitoring method due to its practicality and accuracy. The guideline panel recommended that trough levels should be maintained above 10 mcg/mL for all infections. It also recommended that 15 mcg/mL to 20 mcg/mL is adequate for complicated infections, as this trough is likely to achieve an AUC/MIC > 400 when the organism's MIC is < 1 mcg/mL and the patient has a normal kidney function.[8] However, there were increasing concerns with the use of trough levels as a surrogate for AUC/MIC due to the possible risk of AKI secondary to aggressive dosing, as well as interpatient variability in the correlation between trough levels and target AUC/MIC.[9-11] Experts have expressed that, without a corresponding AUC value, a trough measurement of vancomycin alone is not useful.[12]

There is continuing controversy as to which method is preferable for dosing and monitoring of IV vancomycin for optimal clinical efficacy and avoiding adverse events. The advocacy for using the AUC/MIC ratio method relies on evidence suggesting that trough values above 15 mcg/mL are independently associated with the risk of nephrotoxicity, while quasi-experimental studies suggest the AUC/MIC-based method is linked to lower odds of kidney damage when compared to trough-based monitoring.[13]

The 2020 guidelines on the therapeutic monitoring of vancomycin for serious MRSA infections recommends the AUC/MIC-based method as the preferred approach for therapeutic monitoring of vancomycin.[6] These recommendations were justified based on evidence of the association of better outcomes with the AUC/MIC method, as well as increased failure rates of antimicrobial treatments with the trough-based method, and citing that the challenges and impracticalities of the AUC/MIC method can be overcome with the

use of newer Bayesian software programs and two-level AUC calculators that can make faster and reliable calculations feasible.

As most Canadian hospitals currently use the trough level-based method, implementing the AUC/MIC-based approach will require more resource utilization, such as staff training and software acquisition. An appraisal of quality of the 2020 US guidelines will help inform policy decisions in Canadian hospitals regarding adoption of the AUC/MIC-based approach to optimize dosing of IV vancomycin when treating patients with serious MRSA infection.

Objective

The objective of this CADTH Focused Critical Appraisal (FCA) is to evaluate and summarize the methodological rigour and findings of the clinical practice consensus guideline on the therapeutic monitoring of vancomycin in patients with serious MRSA infections.

Study Under Review

This report includes an assessment and summary with critical appraisal of the following clinical practice guideline: *Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by 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. American Journal of Health-System Pharmacy*. 2020; 77(11):835-864.

Description of the Study — Clinical Practice Guideline

Guideline Objective

The objective of the consensus guideline revision was to evaluate the current scientific data and controversies associated with vancomycin dosing and serum concentration monitoring for serious MRSA infections (defined as "including but not limited to bacteremia, sepsis, infective endocarditis, pneumonia, osteomyelitis, and meningitis"), and to provide updated recommendations based on the available evidence published between 1958 and 2019.[6]

Design and Methods

Organization and Planning

The document is reported as a consensus statement and guideline of the ASHP, the IDSA, the PIDS, and the SIDP. The guideline is a revision of a previous consensus addressing the same topic and published in 2009.[8]

The rationale for creating the current guideline is that new relevant evidence has emerged since the 2009 recommendations were generated, assessing the clinical efficacy and toxicity of vancomycin in patients with serious MRSA infections. This revision aims at evaluating this new evidence and controversies associated with vancomycin dosing and serum concentration monitoring for serious MRSA infections, and provides new recommendations.

The guideline panel consisted of physicians, pharmacists, and a clinical pharmacologist with expertise in clinical practice and research with vancomycin. Panel members were assigned topics related to vancomycin therapeutic monitoring and dosing, but the topics and members assigned to each topic were not reported.

Question and Outcome Generation and Considerations

There is no specific description of the process to generate and assess the importance of the clinical questions addressed by the guideline. Also, no outcome generation process (including ratings of importance) was reported.

Literature Search and Evidence Synthesis

A literature search in PubMed and Embase was conducted using the following search terms: vancomycin, pharmacokinetics, pharmacodynamics, efficacy, resistance, toxicity, obesity, and pediatrics. All relevant and available peer-reviewed studies in the English-language literature published from 1958 through 2019 were considered.

There was no information related to an evidence synthesis process or utilization of evidence syntheses for answering each question. For example, no details were provided as to the study inclusion and exclusion criteria, how many people selected studies for inclusion, or how data were extracted from the included studies. The number of studies excluded from the guideline and reasons for exclusion were not provided.

Assessment of the Evidence

The key evidence obtained that addressed the questions to be discussed was circulated among the committee members. There is no mention if the evidence was prepared by a methodological team or how the information was prepared and synthesized.

The studies assessed for the guideline were rated by their quality of evidence and subsequent recommendations were graded using the Canadian Task Force on the Periodic Health Examination (CTFPHE) system (see Table 1).14 A summary of studies and their findings is provided in supplementary material, but no assessment of the evidence is presented (e.g., risk of bias, pooled effects heterogeneity assessment, etc.).

Table 1: Grading System Used for the Guideline

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 more than 1 centre); 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

Note: Adapted from the Canadian Task Force on the Periodic Health Examination.[14]

Moving from Evidence to Recommendations

The authors went directly from rating the evidence to the corresponding recommendation by using the CTFPHE system. The main process for drafting recommendations is through consensus among committee members and experts, but there is no mention of how the deliberations and decision-making procedures to move from evidence to recommendations were performed.

Reporting and Peer-Review

The guideline went through a review process among all committee members after a first draft was completed. The draft guideline was then available for feedback from the public for a period of 30 days through the ASHP, IDS, PIDS, and SIDP. Following the feedback period, the committee met to review and revise the document based on the submitted comments, suggestions, and recommendations. After discussion and consideration, the document was revised and circulated among the committee and supporting organizations prior to final approval and publication.

Feedback provided on the draft guideline, along with reasons for including or not including the feedback, was not reported.

Plans for Dissemination, Implementation, and Updating

The distribution was made through the official channels of the organizations involved and the main publications of the guideline. No specific plan for dissemination, implementation, or updating is described.

Recommendations

Summary of Recommendations

The guideline presents 25 final primary recommendations for vancomycin dosing and therapeutic drug monitoring (see Appendix 1) divided into three sections according to the population subgroup:

- seven recommendations for both adult and pediatric populations
- nine recommendations for the adult population
- nine recommendations for pediatric populations.

Among the main recommendations are those referring to the preferred method for monitoring and dosing vancomycin in adult patients with suspected or definitive serious MRSA infections, where an individualized target AUC/MIC ratio of 400 to 600 (assuming a vancomycin MIC of 1 mg/L) should be implemented — preferably by using a Bayesian estimation. Meanwhile, trough-based monitoring with a target of 15 mg/L to 20 mg/L is no longer recommended, based on efficacy and AKI data in patients with serious infections due to MRSA (recommendation graded A-II). The guideline panel stated that there was insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA infections such as skin or urinary tract infections, or infections from methicillin-sensitive *S. aureus* or coagulase-negative staphylococci.

The same recommendation is made for pediatric patients regarding vancomycin therapeutic monitoring: AUC-guided therapeutic monitoring, preferably with Bayesian estimation, is suggested for all pediatric age groups. Based on current available data, the suggestion for AUC-guided monitoring in pediatrics aligns with the approach for adults, including the use of a Bayesian estimation for 1 trough concentration (recommendation graded B-II).

Other recommendations included the initial recommended dose and frequency of administration of vancomycin in different subgroups; i.e., adults, children, patients with obesity, patients receiving renal replacement therapy, and hemodialysis patients.

Description of the Evidence for the Recommendations

The evidence used for reaching recommendations regarding the AUC/MIC was from 13 observational studies with clinical outcomes such as bacterial eradication, failure, and mortality. Eleven of the studies were retrospective and 2 were prospective, and sample sizes ranged from 50 patients to 1,300 patients. Additional evidence was identified for other topics including intermittent versus continuous infusion, patients who are obese, and patients receiving renal replacement therapy. There was no formal evaluation or appraisal of these bodies of evidence presented for each recommendation or how the process to move from this evidence to the recommendation was achieved.

Critical Appraisal — Clinical Practice Guidelines

The Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II)[15] was used to evaluate the internal validity of the guideline; that is, the appropriateness of the guideline design and methodology to address the clinical questions and how the body of evidence was used to generate recommendations. The external validity of the guideline, referred to as the applicability of the recommendations reported in the guideline, was assessed by using the Recommendation Excellence supplementary tool (AGREE-REX)[16] of the AGREE II instrument. Three assessors provided the rating for each item of the AGREE instrument and the final score for each domain was discussed and agreed by consensus among assessors. A fourth assessor (information specialist) helped address item 7 (search of evidence) in the AGREE instrument.

The AGREE II assessment is presented in Table 2, with a detailed description in the internal validity section.

Table 2: Quality Assessment of the Guideline Using the AGREE II Instrument

Domain	Item	Ratings[a]	Domain total score — %[b]
1. Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	6	55.56%
	2. The health question(s) covered by the guideline is (are) specifically described.	2	
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5	
2. Stakeholder involvement	4. The guideline development group includes individuals from all relevant professional groups.	4	16.67%
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	1	
	6. The target users of the guideline are clearly defined.	1	
3. Rigour of development	7. Systematic methods were used to search for evidence.	2	29.17%
	8. The criteria for selecting the evidence are clearly described.	2	
	9. The strengths and limitations of the body of evidence are clearly described.	3	
	10. The methods for formulating the recommendations are clearly described.	2	
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	6	
	12. There is an explicit link between the recommendations and the supporting evidence.	2	
	13. The guideline has been externally reviewed by experts prior to its publication	4	
	14. A procedure for updating the guideline is provided.	1	
4. Clarity of presentation	15. The recommendations are specific and unambiguous.	6	94.44%
	16. The different options for the management of the condition or health issue are clearly presented.	7	
	17. Key recommendations are easily identifiable.	7	
5. Applicability	18. The guideline describes facilitators and barriers to its application.	3	16.67%
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	3	
	20. The potential resource implications of applying the recommendations have been considered.	1	
	21. The guideline presents monitoring and/or auditing criteria.	1	
6. Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	1	50.00%
	23. Competing interests of guideline development group members have been recorded and addressed.	7	

[a] Ratings consensus of individual items from three assessors (except on item 7, where a fourth assessor was involved). Each have a minimal value of 1 and a maximum value of 7.

[b] The scaled domain score is calculated as: ([obtained score – minimum possible score] / [maximum possible score – minimum possible]) x 100.

Internal Validity

Scope and Purpose

The general and specific goals of the guideline are well-described, with specific details about the health system needs, as well as the intent and rationale for conducting the guideline. The guideline presents pertinent questions discussed throughout the introduction of the manuscript. However, there is no specific description of the method to generate questions, nor are there details for the process for rating the importance of the questions. A patient/intervention/comparison, or PIC, framework specifying the process for generating questions could improve the search strategy and facilitate the organization and translation of the body of evidence into sensible recommendations.[17-19] Furthermore, no process of outcome generation (and importance rating) was performed.

The populations to which the guideline is meant to be applied are well-described; for example, the guideline focuses on patients with serious MRSA infections, including but not limited to bacteremia, sepsis, infective endocarditis, pneumonia, osteomyelitis, and meningitis. In addition, patient subgroups are discussed in sections throughout the guideline (for example, persons with obesity, kidney failure, pediatric patients). However, the process for determining the subgroups of interest was not described.

Stakeholder Involvement

The guideline development group consisted of a panel of experts that included physicians, pharmacists, and a clinical pharmacologist with expertise in clinical practice and research with vancomycin. The guideline was circulated to the supporting organizations prior to its endorsement, but it's unclear how the approval was obtained. There is no specific mention of target users for this guideline.

Rigour of Development

The methods for obtaining the evidence and crafting recommendations are mentioned in the first part of the guideline. However, some information was not clear or described in detail.

The literature search was conducted in PubMed and Embase, which are appropriate for the search topic. Search limits for date and language are outlined by the authors and are also considered appropriate for the topic and guideline objectives. No additional information is outlined by the authors with respect to a grey literature search.

The search terms are provided broadly; however, there is no additional information available for how the search terms were used, what Boolean operators were applied, whether an appropriate mix of keyword and MeSH headings were considered, and what search fields were selected for each term.

The search as presented in the guideline's methods is not reproducible and cannot be considered comprehensive without further detail or supplementary information. There is no additional information regarding the involvement of an information specialist in developing and executing the search, or of any peer-review conducted on the literature search strategy. Authors of the guideline planned to include both randomized and non-randomized studies. Based on earlier reviews, guidelines, and expert advice, it was expected that limited evidence from randomized trials would be found. However, the specific criteria for including or excluding studies are not described, nor was the assessment process for including studies in the guideline. In addition, the search results, including the number of excluded

studies and the reasons for exclusion, were not described. Lastly, data extraction from the included studies was not described.

The body of evidence that addresses each question or topic for the guideline is narratively described in each topic through the manuscript, albeit more clarification and description is needed about the quality of each body of evidence (strengths and limitations) for each question and outcome. Although it seems that a systematic review was performed for the clinical questions, no pooled effect estimates were produced or reported.

The guideline considers the health benefits, side effects, and risks in the recommendations presented, with a narrative of the evidence when formulating these recommendations. However, there is no mention about the process to produce each clinical recommendation; that is, the steps and rationale to move from evidence to recommendations by considering the net balance of benefits and harms, the quality of the evidence, and the interpretation of these with the values and preferences from patients and other stakeholders, issues of costs, feasibility, and applicability of the interventions. It is assumed that a consensus is reached between experts after discussion but no details were provided.

Authors present each recommendation linked to the quality of evidence and state that the guideline is based mostly on reaching consensus among authors. The system used for rating the evidence and strength of recommendations was one of the first developed systems to rank evidence and classify recommendations.[14] This system provides direct links between the quality of evidence (ranked from I to III) and the strength of recommendations (from A to E). Although the system has been widely adopted because of its simplicity, it doesn't provide details about the quality of evidence, nor considers explicit concerns of harms, balance of harms and benefits, and other items important for decision-making such as feasibility, acceptability, equity, and costs, among others.[20,21]

The guideline was externally reviewed by experts prior to publication. Once finished, it was circulated among committee members and then made available for public comments for 30 days through the ASHP, IDSA, PIDS, and SIDP websites. Then, the final document was revised and circulated among the committee members and supporting organizations prior to final approval and publication. The process for incorporating public feedback was not reported, nor was the amount of feedback received and the reasons for exclusion of feedback, if applicable. In addition, the process for approval was not reported.

No updating procedure or plan to update the recommendations as more evidence is available is described within the guideline.

Clarity of Presentation

The guideline clearly presents the recommendations. Authors supply a precise description of the choice of treatment for the different populations addressed by the guideline. The wording of the recommendations is clear, but there is no clear definition of statements (for instance, the meaning of "suggest" versus "recommend").

The authors clearly present their decisions and expand on the recommendations. For example, there is a good description about the best methods for measuring the AUC/MIC ratio (Bayesian or via calculator). Although the evidence is scarce, a narrative appraisal of the studies is presented before each recommendation.

Finally, the key recommendations are clearly identified through the guideline. These answer the main questions posed by the authors and the guideline panel, and are clearly summarized and identified in tables.

Applicability

The guideline presents arguments in the discussion section of the manuscript around the application of some of the guideline recommendations to facilitate their use and implementation. Barriers and facilitators are the main drivers of this narrative when discussing evidence and recommendations. For example, the authors properly describe the barriers likely to be encountered when implementing the AUC/MIC method, while acknowledging the feasibility and pragmatic application of the trough-based method for monitoring vancomycin administration. However, information on a number of barriers were lacking, including the training of pharmacists to use the software, the training of physicians and nurses to order the correct levels at the correct time for the AUC calculation, or whether feedback was obtained from other stakeholders regarding facilitators and barriers.

No other resources for stakeholders (i.e., manuals, algorithms, online material, etc.) that could facilitate the application of the guideline were provided. Also, no criteria for monitoring or auditing the guideline are presented.

Information about cost-effectiveness of the interventions was not described, as well as the additional resources needed to implement and disseminate the guideline.

Editorial Independence

There is no specific disclaimer about the role of the funding source. Competing interests are well-described at the end of the document, with explicit statements from all members.

External Validity and Quality of Recommendations

The external validity of the guideline and recommendations was assessed using the AGREE-REX, an extension tool for the AGREE II tool.[16] The tool adds three domains including nine items aimed at determining the degree to which guideline authors optimize the quality of recommendations. The assessment is presented in Table 3 and the specific judgments are presented in the text of the external validity and quality of recommendations section.

Table 3: Quality Assessment of the Recommendations Using AGREE REX[16]

Domain	Item	Ratings[a]	Domain total score — %[b]
Clinical applicability	1. Evidence	3	44.45%
	2. Applicability to Target Users	5	
	3. Applicability to Patients/Populations	3	
Values and preferences	4. Values and Preferences of Target Users	1	0%
	5. Values and Preferences of Patients/Populations	1	
	6. Values and Preferences of Policy/Decision-Makers	1	
	7. Values and Preferences of Guideline Developers	1	
Implementability	8. Purpose	3	25.00%
	9. Local Application and Adoption	2	

[a] Ratings of individual items by consensus from three assessors. Each have a minimal value of 1 and maximum of 7.

[b] The scaled domain score is calculated as: ([obtained score – minimum possible score] / [maximum possible score – minimum possible]) x 100.

Clinical Applicability

Clinical applicability of the guideline includes the thoroughness of the process for obtaining the available evidence on which the recommendations are based. In this guideline, the review of the evidence was not explicit enough for detailing the risk of bias from the included studies and other issues, including inconsistent results, imprecision, differences in study populations, and the possibility of confounding factors that could lower the confidence in the results.

When evaluating the applicability to target users — the degree to which the recommendations are applicable to the guideline users' practice context — the guideline addresses the health problem but does not clearly specify the target users of the guideline.

In terms of applicability to patients and populations, the guideline does not assess the extent to which anticipated outcomes of the recommended actions are valued by patients. Although the guideline includes outcomes that are relevant to the specified populations, there was no discussion with patients, nor was there a process to determine the importance of the outcomes.

Values and Preferences

Although the guideline is discussed among the panel of experts and was distributed for feedback to the public after completing the manuscript, the guideline did not formally discuss or obtain the values and preferences of target users (clinicians, pharmacists), patients or patient representatives, policy- or decision-makers (stakeholders of the health system), or from the guideline developers.

Implementability

The guideline recommendations align with the implementation goals of using an AUC/MIC-based method rather than a trough-based method for the therapeutic monitoring of vancomycin. The anticipated impacts of recommendation adoption on individuals, organizations, and health system are briefly described in the discussion section of the guideline, but not expanded or specified to address the suitability of the guideline recommendations for the settings, population, or health care system in which they will be implemented.

In each recommendation, the guideline mentions some issues of local application and adoption related to the administration and monitoring of vancomycin, but it does not discuss the competencies required for AUC/MIC-based monitoring, strategies to overcome barriers associated with changing to AUC/MIC-based monitoring, economic analyses associated with changing from trough-based monitoring to AUC/MIC-based monitoring, or audit criteria that can be used to measure recommendation adherence and improvement in the clinical outcomes of patients.

Summary and Conclusions

The assessed guideline evaluates the current scientific data associated with vancomycin dosing and serum concentration monitoring for serious MRSA infections. The guideline's main recommendation to optimize vancomycin use suggests using the AUC/MIC-based method (targeting a ratio of 400 to 600 and assuming an MIC of 1 mg/L) for the empiric dosing of vancomycin in both adult and pediatric populations to maximize clinical efficacy and minimize the risk of AKI. This recommendation and the quality of evidence were rated as A-II (as defined by the CTFPHE system), meaning that the recommendation is based on "good evidence" from non-randomized studies.

The guideline also provides recommendations and insights about other related topics, such as the initial recommended dosages and infusion of vancomycin in different subgroups; i.e., adults, children, patients with obesity, patients undergoing renal replacement therapy, and hemodialysis. The evidence on these is also of low quality, rated as B-II, B-III, and C-III, as the main source of information comes from observational evidence with a high risk of bias and confounders.

This critical appraisal assessed the guidelines with the AGREE II tool (see Table 2), which shows that the guideline was clear in its presentation of results and recommendations (94.44% score) and moderately clear in the scope and purpose (55.56% score). However, limitations were detected in the acquisition, selection, and evaluation of the evidence that provides the recommendations of the guideline. Specifically, in stakeholder involvement (with a 16.67% final score on this domain), rigour of development (29.17% score), and applicability (16.67% score). For the recommendations, the complementary AGREE-REX tool (Table 3) shows further limitations in the clinical applicability (44.44% score), values and preferences (0%), and implementability of the recommendations (25.00%).

More research to inform the debate between the two vancomycin monitoring options is needed.[12] On one hand, the proponents of continuing the use of the trough-based method claim it is a more practical and low-cost strategy, stating that the collective evidence on AUC-based methods is still hypothesis-generating and inconsistent. On the other hand, the AUC-based monitoring proponents claim it to be a more sophisticated method, with more accuracy and less risk of kidney damage. No information was provided on resource use or the cost-effectiveness of either of these interventions in the reviewed guideline.

This debate reveals how crucial it is to transparently create sensible clinical recommendations based on the best evidence available. As well, it emphasizes the need for considering the balance between benefits and harms, resource use (costs), and implications of the intervention in equity, feasibility, acceptability, and the values and preferences from all stakeholders, especially from patients. This, even when the evidence informing the decisions is scarce or comes from studies with a high risk of bias and uncertainty.

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Appendix 1

Table 4: Primary Recommendations — Clinical Practice Guideline 2020 on Vancomycin Dosing and Therapeutic Monitoring

	RECOMMENDATION
A.	**ADULTS AND PEDIATRIC PATIENTS**
1.	In patients with suspected or definitive serious MRSA infections, an individualized target 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 does not require steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.
3	Trough-only monitoring, with a target of 15 to 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 noninvasive MRSA or other infections.
4	Vancomycin monitoring is recommended for patients receiving vancomycin for serious MRSA infections to achieve a 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 for nephrotoxicity (e.g., critically ill patients receiving concurrent nephrotoxins), patients with unstable (ie, deteriorating or significantly improving) renal function, and those receiving prolonged courses of therapy (more than 3 to 5 days). We suggest the frequency of monitoring be based on clinical judgment; frequent or daily monitoring may be prudent for hemodynamically unstable patients (e.g., those with end-stage renal disease), with 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 greater than 1 mg/L, the probability of achieving an AUC/MIC target of ≥400 is low with conventional dosing; higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment. In addition, when the MIC_{BMD} is less than 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 the 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 of vancomycin with 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 associated risk of 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 2 concentrations (obtained near the steady-state, post-distributional peak concentration at 1 to 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 1 or 2 vancomycin concentrations, with at least 1 trough. It is preferred to obtain 2 PK samples (i.e., 1 to 2 hours post infusion and at the end of the dosing interval) to estimate the AUC with the Bayesian approach **(A-II)**. A trough

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	concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data across different patient populations are needed to confirm the 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 a MIC_{BMD} of 1 mg/L (**A-II**). In patients with normal renal function, these doses may not achieve therapeutic AUC/MIC targets when the MIC is 2 mg/L.
10	*Continuous Infusion*: Based on current available data, a loading dose of 15 to 20 mg/kg, followed by daily maintenance CI of 30 to 40 mg/kg (up to 60 mg/kg), to achieve a target steady-state concentration of 20 to 25 mg/L may be considered for critically ill patients **(B-II)**. AUC24 can be simply calculated when multiplying the steady-state concentration (i.e., desired therapeutic range of 20 to 25 mg/L throughout the 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 CI appears to be similar or lower compared to intermittent dosing when targeting a steady-state concentration of 15 to 25 mg/L and a trough concentration of 10 to 20 mg/L, respectively **(B-II)**. Definitive studies are needed to compare drug exposure based on measured AUC24 and factors that predispose to development of nephrotoxicity, such as receipt of concomitant nephrotoxins, diuretics, and/or vasopressor therapy in patients receiving continuous 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 to 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 3,000 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 to 25 mg/kg using actual body weight, with a maximum of 3,000 mg, may be considered in obese adult patients with serious infections **(B-II)**. Empiric maintenance doses for most obese patients usually do not exceed 4,500 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 4,000 mg/day **(A-II)**.
14	*Intermittent Hemodialysis:* Since efficacy data are unavailable for an AUC of <400 mg • h/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 is likely to achieve the AUC of 400 to 600 mg • h/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 to 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 to 90 minutes of dialysis, as is done with standard hemodialysis **(B-III)**. Concentration monitoring should guide further maintenance doses.
16	*Continuous Renal Replacement Therapy (CRRT):* Loading doses of 20 to 25 mg/kg by actual body weight should be used in patients receiving CRRT at conventional, KDIGO-recommended effluent rates of 20 to 25 mL/kg/h **(B-II)**. Initial maintenance dosing for CRRT with effluent rates of 20 to 25 mL/kg/h should be 7.5 to 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 V_d decreases. The use of CI vancomycin in patients receiving CRRT appears to be growing, and this method could be used in place of intermittent vancomycin dosing, especially when high CRRT ultrafiltrate/dialysate flow rates are employed **(B-II)**.
C	**PEDIATRIC PATIENTS**
17	Based on an AUC target of 400 mg • h/L (but potentially up to 600 mg • hr/L assuming a 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 hours, for children ages 3 months and older **(A-II)**.
18	The maximum empiric daily dose is usually 3,600 mg/day in children with adequate renal function **(C-III)**. Most children generally should not require more than 3,000 mg/day, and doses should be adjusted based on observed concentrations to

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	achieve the AUC/MIC target. Early monitoring of observed concentrations is recommended when doses exceed 2,000 to 3,000 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 5 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 1 trough concentration, or first-order PK equations with 2 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, or those with obesity, or for those receiving concurrent nephrotoxic drug therapy. Following the initial dose, dosing adjustment is important for those with acute renal insuf ficiency, 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 • h/L and for 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 dosages of ≥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 nonobese 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 neonates to adolescents **(C-III)**.
23	*Pediatric Obesity:* Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than in 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 nonobese children, obese children < 12 years old, compared with those ≥ 12 years, may require higher mg/kg doses **(B-II)**.
24	Pediatric Obesity: Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and to minimize the risk of AKI. The specific recommendations for therapeutic monitoring in nonobese 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:* Dosages recommended to achieve an AUC of 400 mg • hr/L (assuming a 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 postmenstrual age, weight, and SCr **(A-II)**.

AKI = acute kidney injury; AUC = area under the curve; BMD = broth microdilution; CL = clearance; ICU = intensive care unit; KDIGO = Kidney Disease Improving Global Outcomes; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; SCr = serum creatinine; Vd = volume of distribution.

Source: Clinical practice guideline on vancomycin monitoring.[6]