Guidelines for Therapeutic Drug Monitoring of Vancomycin: A Systematic Review

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Abstract

Background and Objective: Despite the availability of clinical practice guidelines (CPGs) for therapeutic drug monitoring (TDM) of vancomycin, vancomycin serum concentrations still do not reach therapeutic concentrations in many patients. Thus, we sought to systematically review the quality and consistency of recommendations for an international cohort of CPGs regarding vancomycin TDM.

Methods: PubMed, Embase, guidelines’ websites and Google were searched for CPGs for vancomycin TDM. Two independent assessors rated the quality of each CPG using the Appraisal of Guidelines for Research & Evaluation II (AGREEII) instrument and data were independently extracted.

Results: Twelve guidelines were evaluated and the overall quality of guidelines for vancomycin TDM was moderate. The highest score was recorded in the domain of clarity of presentation, and the lowest score was recorded in the domain of rigor of development and stakeholder involvement. The specific recommendations for vancomycin TDM were moderately consistent and guidelines varied in trough concentration monitoring, frequency of TDM, and serum concentration targets.

Conclusion: The overall guideline quality for vancomycin TDM was not optimal and effort is needed to improve guideline quality, especially in the domain of rigor of development and stakeholder involvement.

Introduction

Vancomycin is a first-line therapy for methicillin-resistant Staphylococcus aureus (MRSA) [1] and this drug is recommended for therapeutic drug monitoring (TDM) to minimize the risk of nephrotoxicity and to ensure successful therapeutic outcomes [2]. To improve the quality of vancomycin TDM, several organizations have developed clinical practice guidelines (CPGs) for appropriate vancomycin TDM. More patients have appropriate trough concentration measurement and sample timing when the guideline is followed [3]. However, many studies suggest that significant numbers of patients do not achieve therapeutic vancomycin serum concentrations [4–13].

CPGs are “statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care option” [14]. Properly developed, high quality CPGs should offer better patient outcomes, reduce risk, and allow cost-effective clinical care [15,16]. However, many CPGs offer poor quality, highly variable recommendations [17–21]. To our knowledge, a systematic evaluation of the quality and the consistency of vancomycin TDM guidelines have not been reported. Thus, the objective of this review was to systematically evaluate the quality and consistency of recommendations for an international cohort of CPGs regarding vancomycin TDM, and in an effort to help develop or update vancomycin TDM guidelines to achieve higher quality recommendations.

Methods

Identification of Guidelines

Guidelines for vancomycin TDM were identified (until June 25, 2013) in PubMed and Embase. Search terms included text words and Medical Subject Headings (MeSH) terms as follows: (“guideline” or “practice guideline” or “guidelines” or “practice guidelines” or “recommendation” or “consensus review” or “guideline” as TopicMeSH) and (“vancomycin” MeSH) and (“therapeutic drug monitoring” or “TDM” or “drug monitoring” or “therapeutic monitoring” or “serum concentration monitoring” or “therapeutic drug” or “drug monitoring” MeSH). Guideline websites and Google were searched to include more relevant CPGs: these included the National Guideline Clearinghouse (www.guideline.gov), Guidelines International Network (www.g-i-n.net/), National Institute for Health and Clinical Excellence (www.nice.org.uk), Scottish Intercollegiate Guidelines Network (www.sign.ac.uk) and China Guideline Clearinghouse (gyc.bjmu.edu.cn:820/). The search term was “vancomycin” and all results were reviewed. Google was searched using the words “vancomycin” and “guideline” and the first 100 items were...
reviewed. To ensure that all potentially relevant guidelines were retrieved, we conducted a search by country in Google and no language restriction was applied.

Selection of Guidelines

CPGs for vancomycin TDM included those that both provided practical clinical recommendations and were endorsed by medical specialty associations, relevant professional societies or governmental agencies. Documents lacking such recommendations and secondary publications were excluded.

Evaluation of Guidelines

Two assessors (Z.K.Y and C.L) used online training tools recommended by the AGREE collaboration before conducting appraisals. Two assessors independently scored each guidelines using AGREE II [22]. AGREE II consists of 23 items organized into six domains: “scope and purpose” (3 items), “stakeholder involvement” (3 items), “rigor of development” (8 items), “clarity of presentation” (3 items), “applicability” (4 items), and “editorial independence” (2 items). Each item is scored from 1 (strongly disagree) to 7 (strongly agree). We referred to methods of a previous study to resolve discrepancies between the two assessors: Briefly, if scores by both assessors differed by two points, they were averaged but if they differed by one point, the lower score was kept. Next, if scores between assessors varied by three points or more, a consensus was reached after a discussion. If consensus was not reached, a third person (S.D.Z) participated in the discussion and resolved the discrepancy [20]. The standard score of each domain was calculated as a percentage of the maximum possible score:

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\text{The scaled domain score} = \left( \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \right)
\]

A score of 50% was chosen to establish the proportion of guidelines which scored greater than or equal to the level in six domains. The overall assessment of included CPGs was based on the overall quality of each guideline.

Synthesis of results

The included CPGs were summarized according to specific recommendations, including indications for TDM, pharmacokinetics-pharmacodynamics, methods of TDM, target of serum concentrations and initial administration plan.

Results

Study selection

Figure 1 shows the study selection process for inclusion in this review. A total of 635 records were retrieved and after application of the inclusion and exclusion criteria, 12 CPGs (AME [23], LOS [24], JAP [25], VAN [26], ALB [27], NHS [28], CAL [29], DEV [30], COR [31], BAT [32], SAP [33], WOR [34]) were included in the review. Table 1 depicts the demographic characteristics for included guidelines. Among the 12 CPGs, three (AME, JAP, NHS) were national CPGs [23,25,28], and the remaining CPGs were regional guidelines. The AME and JAP CPGs were found in medical literature databases [23,25], and the others were found by Google searches. The AME and JAP CPGs rated the quality of evidence and graded the strength of recommendations using the classification schemata of the Canadian Medical Association.

Scope and Purpose

Table 2 shows the standardized scores of each domain and overall recommendation. The mean score for the domain of scope and purpose was 63% (range 28–100%). Nine guidelines scored greater than or equal to 50% [23,25–29,31,33,34], two of them scored greater than or equal to 94% [23,25]. Most guidelines clearly specifically described their scope, related clinical questions and target populations.

Stakeholder Involvement

The mean score for the domain of stakeholder involvement was 27% (range 6–50%). Only three guidelines scored 50% [23,25,31]. No guidelines appeared to include or consider the views or preferences of the target population. Also, members of the guideline development group were not well identified for many guidelines.

Rigor of development

The mean score for the domain of rigor of development was 20% (4–73%). Two guidelines scored above 70% [23,25], the remaining guidelines scored below 20%. Only the AME CPG clearly described the systematic methods for searching evidence [23] and the JAP CPG clearly described the procedure of updating the guideline [25]. No guideline reported their recommendations on an underlying systematic review.

Clarity of presentation

The mean score for the domain of clarity of presentation was 77%. All CPGs scored above 50%. Three CPGs scored greater than 90% [23,25,27]. Most guidelines presented specific, easily identified recommendations for the management of vancomycin TDM.

Applicability

The mean score for the domain of applicability was 47% (range 38–54%). Only four CPGs scored greater than 50% [23,25–27]. No guideline considered the cost of vancomycin TDM, and little information was offered to describe TDM barriers or facilitators.

Editorial independence

The mean score for the editorial independence was 45% (25–67%). Four CPGs scored greater than or equal to 50% [23,25,31,34]. Only the AME and JAP CPGs reported the information about competing interests of guideline development group members [23,25].

Clinical practice guideline recommendations

Indication of TDM. In Table 3, TDM indication reporting is described for the CPGs. Four CPGs (JAP, AME, ALB and VAN) recommended that TDM should be performed in patients receiving aggressive dosing, patients with high risk of nephrotoxicity, unstable renal function, and in those receiving prolonged therapy (more than three or five days). Three CPGs (JAP, VAN and ALB) specifically recommended that TDM should be performed in patients undergoing hemodialysis, those who were obese or had low body weight, those with special conditions that cause fluctuating volumes of distribution, and in pregnant and pediatric patients. The ALB CPG recommended vancomycin TDM should be performed in patients with anticipated therapy of more than two weeks, and the LOS CPG recommended that vancomycin TDM should be performed in patients receiving more than 48 h of vancomycin therapy (Table 3).
Pharmacokinetic and pharmacodynamics monitoring (PK-PD) parameters. Three CPGs (JAP, AME and VAN) recommended that an area under the curve (AUC)/minimum inhibitory concentration (MIC) ratio of more than 400 was associated with clinical efficacy of vancomycin therapy. Trough concentrations were the best surrogates for AUC. Other CPGs did not consider a monitoring parameter associated with clinical efficacy (Table 3).

Peak or trough concentrations. Ten CPGs (JAP, AME, LOS, ALB, NHS, CAL, DEV, BAT, SAP and WOR) recommended monitoring trough concentrations or pre-dose levels rather than peak serum concentrations. The VAN CPG recommended monitoring pre- and post-dose levels to obtain precise pharmacokinetics for some special patients. The COR CPG recommended monitoring peak and trough serum concentrations (Table 3).

Time to first sample. Most CPGs recommended obtaining the first trough sample at steady state (before the 3rd, 4th, or 5th dose in patients with normal renal function). The SAP CPG recommended monitoring troughs within the 48 h of starting therapy. The DEV CPG did not report a time for obtaining the first trough (Table 3).

Frequency of TDM. Five CPGs (AME, JAP, ALB, VAN and DEV) recommended weekly monitoring after initial TDM in patients with normal renal function, and more frequent follow-up trough concentration monitoring was required in patients with hemodynamic instability, high-dose vancomycin administration, unstable renal function, and those at high risk for nephrotoxicity. The LOS CPG recommended more frequent monitoring in patients with complicated infections (goal trough was 15–20 μg/mL) or those with longer courses of therapy. Other CPGs recommended additional drug concentration measurements 4 days or less for patients with normal renal function, and
| Title                                                                 | Year of publication | Country/Region          | Level of development | Organization behind the guideline | Number of authors | Number of references |
|----------------------------------------------------------------------|---------------------|-------------------------|----------------------|----------------------------------|-------------------|----------------------|
| Therapeutic monitoring of vancomycin in adult patients: A consensus  | 2009                | America                 | National             | ASHP/IDSA/SIDP                   | 15                | 129                  |
| review of the American Society of Health-System Pharmacists, the    |                     |                         |                      |                                  |                   |                      |
| Infectious Diseases Society of America, and the Society of Infectious|                     |                         |                      |                                  |                   |                      |
| Diseases Pharmacists (AME) [23]                                      |                     |                         |                      |                                  |                   |                      |
| Vancomycin dosing and monitoring of serum vancomycin levels         | 2013                | Los Angeles             | Regional             | VAGLAHS                          | NR                | 20                   |
| Infectious diseases section guidelines (LOS) [24]                   |                     |                         |                      |                                  |                   |                      |
| Practice guidelines for therapeutic drug monitoring of vancomycin:  | 2013                | Japan                   | National             | JSC/JSTDM                        | 18                | 116                  |
| a consensus review of the Japanese Society of Chemotherapy and the  |                     |                         |                      |                                  |                   |                      |
| Japanese Society of Therapeutic Drug Monitoring (JAP) [25]          |                     |                         |                      |                                  |                   |                      |
| Vancomycin Therapeutic Drug Monitoring Vancouver Coastal Health &   | 2011                | Canada, Vancouver       | Regional             | VCH/PHC                          | 9                 | 7                    |
| Providence Health Care Regional Guideline (VAN) [26]                |                     |                         |                      |                                  |                   |                      |
| Vancomycin Monitoring and Dosing Guideline (ALB) [27]               | 2011                | Canada, Edmonton        | Regional             | AHS                              | NR                | 11                   |
| Vancomycin Guideline for Adults (NHS) [28]                         | NR                  | United Kingdom          | National             | File NHS ADTC                    | NR                | NR                   |
| Prescribing Guidelines for Intravenous Vancomycin in Adults (CAL)   | 2009                | United Kingdom,         | Regional             | CHNHS                            | NR                | 7                    |
| [29]                                                               |                     | Calderdale and          |                      |                                  |                   |                      |
| Huddersfield                                                       |                     |                         |                      |                                  |                   |                      |
| Guidelines on Intravenous (IV) Vancomycin Dosing in Adults (DEV)    | 2010                | United Kingdom,         | Regional             | RDENHS                           | NR                | NR                   |
| [30]                                                               |                     | Devon and Exeter        |                      |                                  |                   |                      |
| Vancomycin prescription and therapeutic drug monitoring guideline   | 2010                | United Kingdom,         | Regional             | RCHNHS                           | 7                 | 3                    |
| (COR) [31]                                                         |                     | Cornwall                |                      |                                  |                   |                      |
| Guidelines for the Dosing and Monitoring of Gentamicin, Vancomycin  | 2009                | United Kingdom,         | Regional             | RUHB NHS                         | NR                | 6                    |
| and Teicoplanin (BAT) [32]                                          |                     | Bath                    |                      |                                  |                   |                      |
| Intravenous Vancomycin Use in Adults Intermittent (Pulsed) Infusion | 2013                | United Kingdom,         | Regional             | SAPG                             | NR                | NR                   |
| (SAP) [33]                                                         |                     | Scottish                |                      |                                  |                   |                      |
| Guidelines for Vancomycin Dosing and Monitoring in Adult Patients   | 2008                | United Kingdom,         | Regional             | WAHNHS                           | 10                | 5                    |
| (WOR) [34]                                                         |                     | Worcestershire          |                      |                                  |                   |                      |

AME: American; ASHP: American Society of Health-System Pharmacists; IDSA: Infectious Diseases Society of America; SIDP: Society of Infectious Diseases Pharmacists; LOS: Los Angeles; VAGLAHS: VA Greater Los Angeles Healthcare System; JAP: Japanese; JSC: Japanese Society of Chemotherapy; JSTDM: Japanese Society of Therapeutic Drug Monitoring; VCH: Vancouver Costal Health; PHC: Providence Health Care; AHS: ALB: Alberta Health Services; NHS: National Health Services; File NHS ADTC: File National Health Services Board Area Drugs and Therapeutics Committee; CAL: Calderdale; CHNHS: Calderdale and Huddersfield NHS; DEV: Devon; RDENHS: Royal Devon and Exeter NHS; COR: Cornwall; RCHNHS: Royal Cornwall Hospitals NHS; BAT: Bath; RUHB NHS: Royal United Hospitals Bath NHS; SAP: Scottish Antimicrobial Prescribing; SAPG: Scottish Antimicrobial Prescribing Group; WOR: Worcestershire; WAHNHS: Worcestershire Acute Hospitals NHS; NR: not reported.
Table 2. AGREE II domain-standardized scores for CPGs on vancomycin TDM.

| Guideline | Scope and Purpose (%) | Stakeholder Involvement (%) | Rigor of development (%) | Clarity and presentation (%) | Applicability (%) | Editorial independence (%) | Overall assessment |
|-----------|-----------------------|-----------------------------|--------------------------|----------------------------|------------------|--------------------------|------------------|
| AME       | 100                   | 50                          | 71                       | 100                        | 54               | 67                       | Recommend        |
| LOS       | 39                    | 6                           | 4                        | 78                         | 38               | 25                       | Not recommend    |
| JAP       | 94                    | 50                          | 73                       | 100                        | 58               | 67                       | Recommend        |
| VAN       | 89                    | 33                          | 13                       | 78                         | 54               | 42                       | Recommend with modification |
| ALB       | 50                    | 17                          | 13                       | 94                         | 54               | 42                       | Recommend with modification |
| NHS       | 28                    | 11                          | 4                        | 61                         | 42               | 33                       | Not recommend    |
| CAL       | 50                    | 11                          | 4                        | 78                         | 42               | 42                       | Not recommend    |
| DEV       | 50                    | 22                          | 8                        | 56                         | 46               | 42                       | Not recommend    |
| COR       | 83                    | 50                          | 13                       | 72                         | 46               | 50                       | Recommend with modification |
| BAT       | 33                    | 17                          | 8                        | 73                         | 46               | 42                       | Not recommend    |
| WOR       | 78                    | 44                          | 19                       | 67                         | 42               | 50                       | Recommend with modification |
| SAP       | 56                    | 17                          | 6                        | 72                         | 46               | 42                       | Not recommend    |
| Mean (Range) | 63 (28–100) | 27 (6–50) | 20 (4–73) | 77 (56–100) | 47 (38–58) | 45 (25–67) | - |

Three CPGs (JAP, LOS and AME) recommended giving a loading dose of 25–30 mg/kg to facilitate rapid attainment of target trough concentrations for serious or complicated infections. Four CPGs (VAN, NHS, DEV and SAP) recommended prescribing a loading dose according to the patients’ actual body weight. Five CPGs (ALB, CAL, COR, BAT and WOR) did not recommend a loading dose (Table 3).

Overall assessment

Two CPGs (AME, JAP) were recommended [23,25], and four CPGs (VAN, ALB, COR and WOR) were recommended with modification [26,27,31,34]. Six CPGs (LOS, NHS, CAL, DEV, BAT and SAP) were not recommended. The two CPGs that were recommended have a higher score in domain of rigor of development and a standard search strategy, and they classified the quality of evidence and graded the strength of recommendations. The six CPGs that were not recommended scored below 10% in the domain of rigor of development and the other domains’ scores was not high.

Discussion

To our knowledge, this is the first study to evaluate the quality and consistency of vancomycin TDM guidelines; although, CPG quality has been investigated in a variety of clinical areas [17–21]. We made three important findings: first, the overall guideline quality was moderate, and more efforts are needed to improve these guidelines, especially with respect to the domain of rigor of development and stakeholder involvement. Second, vancomycin TDM guideline recommendations were moderately consistent. Third, regional guidelines were of lower quality than national guidelines. In the United Kingdom and Canada, national guidelines may be of sufficient quality to replace regional guidelines of those areas.

Guidelines consistently scored well with respect to clarity and presentation, suggesting that this domain may be easier to achieve or may be more highly emphasized by guideline developers. The
Table 3. Recommendations from CPGs.

| Item                          | AME | LOS | JAP | VAN | ALB | NHS | CAL | DEV | COR | BAT | SAP | WOR |
|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Indication of TDM             | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  |
| PK–PD parameter               | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  | NR  |
| Method of TDM                 |     |     |     |     |     |     |     |     |     |     |     |     |
| Peak or trough concentration  | trough | trough | trough | Pre–levels and post–levels | trough | trough | Pre–dose levels | Pre–dose levels | Peak and trough | Pre–dose levels trough | trough |
| Time for trough sample        | Within 30 min | NR | Within 30 min | NR | Within 30 min | NR | NR | Within 60 min | NR | NR | NR | NR |
| Time to first level (patients with normal renal function) | Before 4th dose | Before 5th dose | Before 4th or 5th dose | not earlier than 3rd dose and within 48 h | After at least two dose | before 2nd maintenance dose | Before 3rd, 4th, or 5th dose | NA | before 3rd or 4th dose | Before 3rd or 4th dose | within 48 h of starting therapy | Before 3rd, 4th dose |
| Frequency of TDM (patients with normal renal function) | weekly | Depend on clinical condition | weekly | weekly | weekly | Twice weekly | Twice weekly | weekly | After 4 days | Twice weekly | Every 2-3 days | Every 3-4 days |
| Target of trough concentration (µg/mL) | 10–20 | 10–20 | 10–20 | Lower than 20 | 5–20 | 10–20 | 10–20 | 10–15 | 5–15 | 10–20 | 5–15 |
| Target trough concentration in complicated infections | 15–20 | 15–20 | 15–20 | 15–20 | 10–20 | 15–20 | 15–20 | NR | NR | 10–15 | 15–20 | Higher levels* |
| Loading dose | 25–30 mg/kg | 25–30 mg/kg | 25–30 mg/kg | (ma >2,500 mg/dose) | NR | Loading dose | NR | Loading dose | NR | Loading dose | NR |

NR: not reported.

*Higher levels may be required in specific situations as directed by the microbiologist.

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lowest score was recorded in rigor of development, perhaps due to the fact that most guidelines did not report the systematic methods for evidence searching, and many had poorly described information about selection criteria, evidential strengths and limitations, and procedures for updating guidelines. The AME and JAP CPG had the highest scores in this domain and all rated the quality of evidence and graded the recommendation strength, indicating that using a formal system might improve scores for developmental rigor. Developmental rigor is closely related to guideline quality and guideline developers should pay more attention to this domain. The mean score for stakeholder involvement was 27%. No guidelines have considered the views and preferences of patients or of the public, but patient involvement in decision making about care management may improve physician and patient guideline adherence and improve clinical outcomes [35].

The mean score for applicability was 47%, and only four guidelines scored greater than 50% in this area. No guideline considered the cost of vancomycin TDM and no guideline provided enough evidence to support the necessity of vancomycin TDM. Guideline developers did not address potential barriers of guideline implementation and this may have contributed to many hospitals not monitoring vancomycin serum concentrations and many patients not achieving target therapeutic concentrations. The mean score for the scope and purpose was 63%, and most guidelines described their scope, related clinical questions and target populations well. The mean score for editorial independence was 45%. No guidelines described funding sources, although they were developed by medical societies. Most guidelines did not offer data regarding competing interests among guideline development group members. Guideline developers should emphasize these points in future studies.

Specific recommendations of vancomycin TDM guidelines were moderately consistent and varied with respect to trough concentration monitoring, TDM frequency and target serum concentrations across guidelines, which was possibly attributed to unique references for each guideline and only two guidelines (AME, JAP) describing their systematic search strategy. Also, few prospective or randomized trials for vancomycin TDM were available and most of the published literature regarding vancomycin monitoring are observational studies.

The AME and JAP CPG rated the quality of evidence and graded recommendations using the same classification schemata recommended by the Canadian Medical Association. However, evidence and strength of recommendations were inconsistent, and this may be attributed to the search strategy, criteria for selecting evidence, methods for formulating recommendations, and experts’ consensus [36]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for rating the quality of evidence and grading the strength of recommendations is increasingly being adopted by organizations because this rating system is explicit, comprehensive, transparent and pragmatic [37]. We advise guideline developers to adopt GRADE for this reason.

Our search identified all potentially relevant studies but limitations of our approach included the fact that included CPGs were written in English or Chinese. So other CPGs written in other languages were likely missed, even though no restriction on language was applied. Second, AGREE II did not provide criteria about the overall assessment to guide assessors in determining scores, so two assessors may fail to properly weigh domain scores.

In conclusion, the overall quality of vancomycin TDM guidelines was moderate and warrant improvement. Specifically, rigor of development and stakeholder involvement would benefit from increased scrutiny. Guideline recommendations were moderately consistent, especially with respect to regional guidelines. Local adaptation of existing high-quality CPGs to national use is worth considering and a national, high quality guideline to replace various regional guidelines would avoid duplicate efforts. The developers of guidelines should adhere more closely to the AGREE instrument when developing or updating vancomycin TDM guidelines.

Supporting Information

Checklist S1  PRISMA 2009 Checklist.doc.

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Author Contributions

Conceived and designed the experiments: ZKY SDZ. Performed the experiments: ZKY CL. Analyzed the data: ZKY CL. Contributed reagents/materials/analysis tools: ZKY CL. Wrote the manuscript: ZKY. Revised the manuscript: ZKY CL SDZ. Approved the final version of the manuscript: ZKY CL SDZ.

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