

Vancomycin Therapeutic Drug Monitoring: A Cross-Sectional Survey of Canadian Hospitals

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ABSTRACT

Background: Little is known about the current landscape of vancomycin therapeutic drug monitoring (TDM) in Canadian hospitals, which operate within publicly funded health care systems.

Objectives: To determine current TDM practices for vancomycin and associated challenges and to gather perceptions about TDM based on area under the concentration–time curve (AUC) in Canadian hospitals.

Methods: An electronic survey was distributed to hospital pharmacists in spring 2021 through multiple national and provincial antimicrobial stewardship, public health, and pharmacy organizations. The survey gathered data about hospital characteristics, TDM methods, inclusion criteria for patient selection, pharmacokinetic and pharmacodynamic targets, vancomycin susceptibility testing and reporting, and perceived barriers and challenges.

Results: In total, 120 pharmacists from 10 of the 13 provincial and territorial jurisdictions in Canada, representing 12.5% of Canadian acute care hospitals ($n = 962$), completed at least 90% of survey questions. The predominant TDM method was trough-based (107/119, 89.9%); another 10.1% of respondents (12/119) reported performing AUC-based TDM (with or without trough-based TDM), and 17.9% (19/106) of those not already using AUC-based TDM were considering implementing it within 1 to 2 years. Among hospitals performing trough-based TDM, 60.5% (66/109) targeted trough levels between 15 and 20 mg/L for serious infections with methicillin-resistant *Staphylococcus aureus*. One-quarter of the respondents using this method (27/109, 24.8%) agreed that trough-based TDM was of uncertain benefit, and about one-third (33/109, 30.3%) were neutral on this question. Multiple challenges were identified for trough-based TDM, including sub- or supra-therapeutic concentrations and collection of specimens at inappropriate times. Overall, 40.5% (47/116) of respondents agreed that AUC-based TDM was likely safer than trough-based TDM, whereas 23.3% (27/116) agreed that AUC-based TDM was likely more effective.

Conclusions: This survey represents a first step in developing evidence-based, standardized best practices for vancomycin TDM that are uniquely suited to the Canadian health care system.

Keywords: vancomycin, therapeutic drug monitoring, area under the curve, trough, survey

RÉSUMÉ

Contexte : On connaît peu de choses sur le paysage actuel du suivi thérapeutique pharmacologique (STP) de la vancomycine dans les hôpitaux canadiens, dont les activités s'inscrivent dans le cadre des systèmes de soins de santé financés par les deniers publics.

Objectifs : Déterminer les pratiques actuelles de STP de la vancomycine et les défis associés et recueillir les perceptions concernant le STP sur la base de l'aire sous la courbe de la concentration en fonction du temps (ASC) dans les hôpitaux canadiens.

Méthodes : Un sondage a été distribué électroniquement aux pharmaciens d'hôpitaux au printemps 2021 par plusieurs organismes nationaux et provinciaux de gestion de l'utilisation des antimicrobiens, de santé publique et de pharmacie. Le sondage a permis de rassembler des données concernant les caractéristiques des hôpitaux, les méthodes de STP, les critères d'inclusion pour la sélection des patients, les objectifs pharmacocinétiques et pharmacodynamiques, les tests de sensibilité à la vancomycine et les rapports des résultats, ainsi que les obstacles et les défis perçus.

Résultats : Au total, 120 pharmaciens de 10 des 13 provinces et territoires du Canada, représentant 12,5 % des hôpitaux canadiens de soins actifs ($n = 962$), ont répondu à au moins 90 % des questions du sondage. La méthode de STP prédominante utilisée était celle de la concentration minimale (107/119, 89,9 %); un autre 10,1 % des répondants (12/119) ont déclaré effectuer un STP basé sur l'ASC (avec ou sans STP basé sur la concentration minimale), et 17,9 % (19/106) de ceux qui n'effectuaient pas déjà le STP basé sur l'ASC envisageaient de le mettre en œuvre d'ici 1 à 2 ans. Parmi les hôpitaux pratiquant le STP basé sur la concentration minimale, 60,5 % (66/109) ciblaient des concentrations minimales entre 15 et 20 mg/L pour les infections graves à *Staphylococcus aureus* résistant à la méthicilline. Un quart des répondants qui utilisaient cette méthode (27/109, 24,8 %) convenaient que les avantages du STP basé sur la concentration minimale étaient incertains, et environ un tiers (33/109, 30,3 %) étaient neutres. De multiples défis ont été identifiés pour le STP basé sur la concentration minimale, notamment des concentrations sous- ou supra-thérapeutiques et la collecte d'échantillons à des moments inappropriés. Dans l'ensemble, 40,5 % (47/116) des répondants convenaient que le STP basé sur l'ASC était probablement plus sûr que le STP basé sur la concentration minimale, tandis que 23,3 % (27/116) convenaient que le STP basé sur l'ASC était probablement plus efficace.

Conclusions : Ce sondage représente une première étape dans l'élaboration de pratiques exemplaires normalisées et fondées sur des données probantes pour le STP de la vancomycine qui sont particulièrement adaptées au système de santé canadien.

Mots-clés : vancomycine, suivi thérapeutique pharmacologique, aire sous la courbe, concentration minimale, sondage

INTRODUCTION

For decades, vancomycin has been the standard treatment for serious infections caused by gram-positive bacteria.¹ Its narrow therapeutic index, coupled with pharmacokinetic variability, has made it a primary focus of inpatient therapeutic drug monitoring (TDM) services.² Yet despite more than 60 years of clinical use and a vast body of research investigating vancomycin pharmacokinetics and pharmacodynamics, the optimal dosing and TDM strategy remains unclear. This situation is concerning, given that dose optimization is a key antimicrobial stewardship strategy to maximize efficacy, minimize adverse effects, and slow the emergence of antimicrobial resistance.³

To address this uncertainty and to standardize practice, in 2009 the Infectious Diseases Society of America (IDSA), the American Society of Health-System Pharmacists (ASHP), and the Society of Infectious Diseases Pharmacists (SIDP) published guidelines for vancomycin dosing and TDM.² A key recommendation was to use more aggressive dosing for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections, targeting a value of at least 400 for the ratio of area under the concentration–time curve (AUC) over 24 hours to minimum inhibitory concentration (MIC) and using a trough range of 15 to 20 mg/L as a practical surrogate.² At that time, it was concerns about the emergence of *S. aureus* strains with reduced vancomycin susceptibility and reports of treatment failure in patients infected with *S. aureus* isolates having higher vancomycin MIC that prompted the guideline authors to advocate for more aggressive dosing, despite the absence of supporting clinical evidence.^{4,5} However, since publication of the guidelines in 2009, data have become available indicating that higher trough levels are associated with a greater risk of nephrotoxicity without any improvement in effectiveness.^{6,7}

Given the well-documented harms associated with high vancomycin trough concentrations,^{6,7} the updated IDSA/ASHP/SIDP vancomycin guidelines, published in 2020, do not include this recommendation and instead recommend transitioning to AUC-guided TDM.⁸ This form of TDM can be accomplished with Bayesian modelling software (preferred), 2-point pharmacokinetic–pharmacodynamic equations, or population-based pharmacokinetic–pharmacodynamic estimates.⁸ Several observational studies have reported reduced nephrotoxicity after implementation of AUC-based TDM.^{9,10} However, other studies, in which vancomycin dosing, exposure, and duration were more balanced between groups, did not report differences in nephrotoxicity.^{11,12} Additionally, clinical data supporting AUC/MIC ≥ 400 as predictive of efficacy have been of poor quality and inconsistent, which has prompted others to suggest that widespread adoption of AUC-based TDM may be premature.^{13–16} The resources required to support AUC-based dosing and opportunity costs are additional considerations. Furthermore, proprietary or

subscription-based Bayesian software may be cost-prohibitive in many health care settings. Alternative methods, such as 2-point pharmacokinetic–pharmacodynamic equations, require multiple, precisely timed patient blood samples coupled with a considerable investment of pharmacy, laboratory, and nursing resources.

Little is known about the current landscape of vancomycin TDM in Canadian hospitals, which operate under publicly funded health care systems. To address this gap, we conducted a national survey of Canadian acute care hospitals. Our primary objectives were to determine current vancomycin TDM practices and associated challenges and to gather perceptions about AUC-based TDM.

METHODS

We developed an electronic survey based on an environmental scan of vancomycin TDM practices in Canadian hospitals, input from stakeholders, and previous surveys conducted in the United States.^{17–19} The online survey, provided in English only, was developed using REDCap (Research Electronic Data Capture, Vanderbilt University, hosted at the University of Toronto)²⁰ and can be viewed at <https://redcap.utoronto.ca/surveys/?s=T7FWJJPMXT>. We piloted the survey with pharmacists at Mount Sinai Hospital, Toronto, Ontario, and modified it on the basis of their feedback. We distributed an introductory letter and link to the survey through the Canadian Society of Hospital Pharmacists' newsletter, the Antimicrobial Stewardship Hospital Pharmacists in Ontario Network, the Public Health Ontario email listserv, and personal email messages to antimicrobial stewardship pharmacists across Canada who were known to the authors. We provided instructions that the survey should be completed by 1 pharmacist per hospital, preferably the antimicrobial stewardship pharmacist. The survey was open for 8 weeks (March 8 to May 3, 2021). Results and interpretation are reported according to the CHECKlist for Reporting Results of Internet E-Surveys (CHERRIES).²¹

The Mount Sinai Hospital Research Ethics Committee approved the survey. There were no monetary incentives to participate. Respondents were informed that consent was implied by survey submission.

We used descriptive statistics to summarize the data. We used IBM SPSS Statistics for Windows, version 27.0, for all calculations.

RESULTS

In total, 120 pharmacists from 10 of the 13 provincial and territorial jurisdictions, representing 12.5% of acute care hospitals in Canada ($n = 962$), completed at least 90% of the survey questions. The highest provincial representation was from Ontario and New Brunswick (20.5% and 22.7%, respectively) (Table 1). Responding hospitals were

predominantly university-affiliated (97/120, 80.8%) and located in urban centres (91/120, 75.8%), and most had a formal antimicrobial stewardship program (101/120, 84.2%) (Table 2). At least 1 full-time equivalent antimicrobial stewardship or infectious diseases pharmacist was employed at approximately half (62/120, 51.7%) of responding hospitals. The predominant pharmacy model was decentralized (62/120, 51.7%).

At more than half of the hospitals represented (69/120, 57.5%), pharmacists only or pharmacists and physicians were primarily responsible for vancomycin TDM; the majority (96/119, 80.7%) of respondents reported having a medical directive to order serum vancomycin concentrations and/or adjust doses autonomously. Institution-specific vancomycin TDM guidelines had been developed by many hospitals (99/120, 82.5%), and specific training or credentialing for pharmacists was required to perform vancomycin TDM at more than half (73/119, 61.3%). TDM was routinely performed for patients with risk factors for nephrotoxicity (117/119, 98.3%), confirmed or suspected invasive gram-positive infections (114/119, 95.8%), anticipated duration of vancomycin therapy at least 5 (\pm 2) days (112/119, 94.1%), and critical illness (104/114, 91.2%). However, most respondents (105/119, 88.2%) reported that TDM was “always” or “sometimes” performed for short courses of therapy (less than 5 days) for patients with stable renal function. The predominant method of vancomycin administration was intermittent infusion (104/119, 87.4%); a few respondents (14/119, 11.8%) reported using continuous infusions for selected patient populations.

With regard to testing and reporting of susceptibility of *S. aureus* to vancomycin, approximately half of hospital laboratories (61/120, 50.8%) reported interpretive susceptibility

criteria only (i.e., no specific MIC was reported). Nearly half (51/120, 42.5%) of respondents were unsure of the method that their laboratory used to determine the MIC of vancomycin against *S. aureus*. Among respondents who did know this information, Vitek-2 (Bio-Mérieux Canada) was the most commonly used automated platform (51/69, 73.9%); vancomycin MICs for *S. aureus* specimens taken from sterile sites were confirmed using gradient test strips by about half (37/69, 53.6%) of laboratories.

TABLE 1. Representation of Canadian Hospitals by Province or Territory

Province or Territory ^a	No. of Hospitals ^b	No. (%) of Respondents
Ontario	268	55 (20.5)
Quebec	170	12 (7.1)
British Columbia	126	15 (11.9)
Alberta	132	10 (7.6)
Manitoba	61	7 (11.5)
New Brunswick	44	10 (22.7)
All other jurisdictions ^c	161	11 (6.8)
Total	962	120 (12.5)

^aListed in descending order of number of hospitals.

^bNumber of hospitals in 2019, as reported in the Government of Canada's Canadian industry statistics.²²

^cProvinces and territories with fewer than 6 respondents were grouped to protect anonymity.

TABLE 2. Hospital and Pharmacy Characteristics

Characteristic	No. (%) of Respondents (n = 120)
Geographic location	
Urban	91 (75.8)
Rural	29 (24.2)
Type of hospital	
Academic	47 (39.2)
Community, teaching	52 (43.3)
Community, nonteaching	21 (17.5)
Hospital's university affiliation	
Medical and pharmacy schools	56 (46.7)
Pharmacy school only	5 (4.2)
Medical school only	36 (30.0)
None	23 (19.2)
Predominant patient population served	
Inpatient mixed	114 (95.0)
Inpatient oncology	0
Inpatient continuing complex care	4 (3.3)
Inpatient other	2 (1.7)
Formal antimicrobial stewardship program	101 (84.2)
Antimicrobial stewardship pharmacist (no. of FTEs)	
0	35 (29.2)
0.5–0.75	23 (19.2)
1	40 (33.3)
2	16 (13.3)
\geq 3	6 (5.0)
Pharmacy model	
Centralized	58 (48.3)
Decentralized	62 (51.7)
Pharmacy residency program	60 (50.0)
Respondent's position	
Antimicrobial stewardship or infectious diseases pharmacist	86 (71.7)
Internal medicine pharmacist	13 (10.8)
Critical care pharmacist	8 (6.7)
Pharmacy manager	3 (2.5)
Other ^a	10 (8.3)

FTE = full-time equivalent.

^a“Other” consisted of 4 staff pharmacists, 1 clinical resource pharmacist, 1 clinical coordinator, 1 professional practice lead, 1 family medicine pharmacist, 1 antimicrobial stewardship/critical care/medicine pharmacist, and 1 multifunctional pharmacist.

The predominant TDM method was trough-based (107/119, 89.9%), with smaller proportions of respondents reporting use of AUC-based TDM (9/119, 7.5%) or a mix of AUC- and trough-based TDM (3/119, 2.5%). Among those not currently using AUC-based TDM, nearly one-fifth (19/106, 17.9%) were considering implementing AUC-based TDM within 1 to 2 years; a further two-fifths (43/106, 40.6%) were unsure about making the transition. In hospitals performing trough-based TDM, target vancomycin troughs for serious *S. aureus* infections (e.g., bacteremia, infective endocarditis, pneumonia, bone and joint infections) were commonly between 15 and 20 mg/L (66/109, 60.5%) or between 10 and 20 mg/L (19/109, 17.4%). By contrast, the majority of respondents (78/110, 70.9%) reported targeting 10 to 15 mg/L for noninvasive infections (e.g., skin and soft tissue infections). Respondents identified multiple challenges associated with trough-based TDM. Most respondents agreed or strongly agreed that collection of specimens at inappropriate times (83/110, 75.5%) and supra- or sub-therapeutic concentrations (80/109, 73.4%, and 60/109, 55.0%, respectively) were major challenges, but less than one-quarter (26/110, 23.6%) identified cost as a barrier. Overall, one-quarter (27/109, 24.8%) of respondents agreed or strongly agreed that trough-based TDM was of uncertain benefit; about one-third (33/109, 30.3%) had a neutral opinion on this question.

Of the 12 hospitals currently using AUC-based TDM, 10 were located in Quebec, 1 in Ontario, and 1 in Manitoba. Eight were located in urban centres, and 11 had a university affiliation. Publicly available Bayesian modelling software was used by 6 of the hospitals, the 2-sample trapezoidal method by 5, and population pharmacokinetic equations by 1. All of these hospitals targeted an AUC/MIC therapeutic range of 400 to 600, although 2 further qualified their ideal target as 400 to 515. For the purposes of TDM, the vancomycin MIC for *S. aureus* was assumed to be 1 mg/L at 7 hospitals.

Among hospitals considering or unsure about making the transition to AUC-based TDM, just over half (32/61, 52.5%) did not currently have a preference for the method to estimate AUC; others favoured publicly available Bayesian software (16/61, 26.2%) or the 2-sample trapezoidal method (11/61, 18.0%), and a small proportion (2/61, 3.3%) were considering using proprietary or subscription-based Bayesian software. Among hospitals that were *not* currently using AUC-based TDM, the most commonly anticipated challenges in adopting this approach were lack of physician familiarity (95/104, 91.3%), need for training (94/104, 90.4%), requirement for multiple concentrations (84/103, 81.6%), need for laboratory and nursing resources (79/104, 76.0%), collection of specimens at inappropriate times (77/104, 74.0%), allocation of pharmacists' time (77/104, 74.0%), cost (66/102, 64.7%), and potential errors (66/104, 63.5%). Interestingly, among hospitals that *were* currently using AUC-based TDM, allocation of

pharmacists' time, need for laboratory and nursing resources, lack of physician familiarity, and cost were perceived as challenges by less than 30% of respondents. Collection of specimens at inappropriate times and the requirement for multiple specimens (8/12, 66.7%, and 7/12, 58.3%, respectively) were the major challenges reported by those already using AUC-based TDM.

Overall, only two-fifths (47/116, 40.5%) of respondents agreed or strongly agreed that AUC-based TDM was likely safer than trough-based TDM; a smaller proportion (27/116, 23.3%) agreed or strongly agreed that AUC-based TDM was likely more effective. By contrast, among respondents whose hospitals had already implemented AUC-based TDM, most (11/12, 91.7%) agreed or strongly agreed that it was safer and half (6/12, 50.0%) agreed or strongly agreed that it was more effective than trough-based TDM.

DISCUSSION

To the best of our knowledge, this survey represents the first broad assessment of vancomycin TDM in Canadian hospitals. Our sample included respondents from a wide range of rural and urban centres representing approximately 1 of every 8 acute care hospitals across 10 provincial and territorial jurisdictions in Canada. The survey revealed several important aspects of current TDM practices for vancomycin. Notably, although Canada does not have national guidelines to define best practices for vancomycin TDM, we found remarkably low variability across centres in certain TDM practices. Approximately 90% of hospitals participating in the survey performed trough-based TDM, intermittent infusions were the predominant administration method, and nearly two-thirds of hospitals targeted troughs between 15 and 20 mg/L for serious MRSA infections. This latter finding is troubling, given the overwhelming evidence that high vancomycin troughs are associated with increased rates of nephrotoxicity without improvements in effectiveness.^{6,7} The updated vancomycin guidelines, released more than 12 months before we distributed our survey, were specifically revised to omit the recommendation to target high troughs, citing safety concerns.⁸ However, as has been observed in multiple areas of medicine, once something is ingrained in clinical practice, de-adoption is a slow and difficult process.²³ Moving forward, we must commit to abandoning interventions that have been shown to be of no benefit to patients and are actually harmful.

Implementing accurate and clinically valuable TDM services is complex and involves coordination across multiple disciplines. It should not be surprising that pharmacists responding to this survey identified many challenges with trough-based TDM that have been repeatedly documented in the literature: trough results above or below the therapeutic range, collection of specimens at inappropriate times, the need for pharmacist training, and allocation of

time for this work.²⁴ These challenges were not counter-balanced by positive assessments of the value of TDM. Nearly one-quarter of pharmacists responding to the survey agreed that trough-based TDM was of uncertain benefit, and approximately one-third were neutral. Despite what appears to be prevalent uncertainty, nearly 90% of respondents reported routinely performing vancomycin TDM for patients receiving short courses of therapy without risk factors for nephrotoxicity, a population unlikely to derive any benefit from this practice. Standards of practice, adapted from clinical guidelines, or institutional protocols can sometimes promote “defensive medicine” motivated by fear of liability. Our findings reveal a need to support pharmacists if they deviate from expected practice when patient-specific considerations suggest that a different therapeutic approach may be preferred. The prevalences of MRSA and other multidrug-resistant (MDR) gram-positive bacteria are relatively low in Canada (16.9% for MRSA and 7.7% for MDR *Streptococcus pneumoniae*, as of 2016)^{25,26}; most patients may be better served by early vancomycin discontinuation, rather than TDM of an unneeded drug.

An obvious follow-up question is “How can we improve upon current vancomycin TDM practices?” Very few hospitals in our survey had transitioned to AUC-based TDM, and only 17.9% were planning to make the transition in the near future. These results appear to be driven by both uncertainty about the benefits and anticipation of multiple challenges relating to resource use, opportunity costs, and buy-in from relevant stakeholders. A survey of inpatient hospitals in the United States, conducted shortly before the updated guidelines were released, reflected similar uncertainty.¹⁷ Among 78 hospitals surveyed, less than one-quarter reported performing AUC-based vancomycin TDM.¹⁷ Nearly 90% of hospitals performing trough-based TDM did not plan to transition to AUC-based TDM within the next year or were uncertain about doing so. In a more recent US survey ($n = 202$), approximately 70% of respondents had not implemented AUC-based TDM, but over half were planning to do so within the next year.¹⁹ Interestingly, in our survey, respondents from institutions that *had* already implemented AUC-based TDM did not perceive many of the challenges anticipated at other hospitals as being relevant, and their certainty about the safety benefit was nearly unanimous.

This survey had several limitations. Respondents represented predominantly university-affiliated medical centres with established antimicrobial stewardship and pharmacy residency programs. Several provinces were overrepresented, and others were underrepresented. Most respondents were antimicrobial stewardship or infectious diseases pharmacists; their responses may not be generalizable to pharmacists not specializing in antimicrobial stewardship or infectious diseases, and responses might vary from one pharmacist to another at the same site. Although the survey instructions requested that only 1 pharmacist

from each hospital complete the survey, it is possible that more than 1 pharmacist from the same health region, governed by the same practice standards, were included. We focused on vancomycin TDM in adult inpatients, but additional research is needed to understand TDM practices for other populations, including pediatric patients, neonates, outpatients, and residents of nursing homes or rehabilitation facilities. Because we used multiple methods to distribute the survey, which covered overlapping populations, we were unable to calculate a denominator to determine the response rate or assess response bias. We used national hospital numbers as an imperfect proxy for gauging the reach of our survey. Finally, the response period for our survey partly coincided with the devastating third wave of the COVID-19 pandemic in Canada. Response rates from harder-hit hospitals were likely depressed, and the study team’s attention was diverted from promoting the survey. Moreover, plans to implement vancomycin AUC-based TDM may have been delayed because of the pandemic.

CONCLUSION

Understanding the current landscape of vancomycin TDM across Canada, as well as the challenges experienced by pharmacists performing TDM, is a first step in developing evidenced-based, standardized best practices that are uniquely suited to Canadian health care. Concerns have been raised about the quality and consistency of the evidence supporting AUC-based vancomycin TDM.¹⁴⁻¹⁶ Prematurely adopting AUC-based TDM before it has been proven to work (through appropriately designed clinical trials) and shown to be feasible in Canadian hospitals risks diverting resources from other higher-yield interventions. In the meantime, de-adopting high trough targets should be a patient safety priority. Vancomycin is one of the most commonly used antimicrobials for hospitalized patients; generating robust evidence to guide its optimal use is our next step and should be a priority for funding agencies.

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