

Review Article

Therapeutic Drug Monitoring and Pharmacokinetics-Based Individualization of Drug Therapy: Canadian Practice and the Transition to Model-Informed Precision Dosing

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	RECEIVED	REVISED	ACCEPTED	PUBLISHED ONLINE
	01 JUNE 2026	10 JUNE 2026	15 JUNE 2026	18 JUNE 2026

Citation details: Mohamed Abdellatif, et al. (2026). Therapeutic Drug Monitoring and Pharmacokinetics-Based Individualization of Drug Therapy: Canadian Practice and the Transition to Model-Informed Precision Dosing. International Journal of Clinical Pharmacy and Medicine, 1(1), Article 2.

Abstract

Background: Therapeutic drug monitoring (TDM) has traditionally relied on measured serum concentrations interpreted against predefined therapeutic ranges. This approach remains valuable for medications with narrow therapeutic indices but may inadequately account for substantial interindividual pharmacokinetic variability. Model-informed precision dosing (MIPD), particularly Bayesian forecasting, provides a framework for integrating drug concentrations with population pharmacokinetic models and patient-specific characteristics to individualize therapy.

Objective: To review contemporary TDM and pharmacokinetics-based dose individualization, with particular attention to Canadian practice and the transition from conventional concentration monitoring toward model-informed precision dosing.

Methods: A narrative review of contemporary pharmacokinetic literature, therapeutic monitoring guidance, Canadian hospital studies, institutional surveys, and studies evaluating Bayesian and model-informed dosing was undertaken.

Results: Canadian experience demonstrates both the established role of pharmacist-led TDM and important opportunities for modernization. In a national survey of 120 pharmacists from 10 Canadian provincial and territorial jurisdictions, approximately 90% of hospitals still used trough-based vancomycin monitoring, whereas only 10.1% reported AUC-based monitoring. Most hospitals had institutional vancomycin guidelines, and 80.7% reported medical directives allowing pharmacists to order concentrations and/or adjust doses autonomously. Canadian institutions have also developed open-source Bayesian vancomycin tools, investigated aminoglycoside monitoring practices, evaluated beta-lactam concentrations in critically ill patients, and optimized tacrolimus monitoring through pharmacist-led protocols. These examples illustrate the progression from concentration measurement toward individualized exposure-guided therapy.

Conclusion: TDM is evolving from interpretation of isolated drug concentrations toward individualized pharmacokinetic decision-making. Canadian experience highlights both strong pharmacist involvement and substantial variability in implementation. Wider adoption of MIPD will require validated models, clinical decision-support infrastructure, pharmacist training, integration with electronic health records, appropriate laboratory support, and evidence that improved exposure target attainment translates into meaningful patient outcomes.

Keywords: Therapeutic drug monitoring; model-informed precision dosing; Bayesian dosing; Canada; vancomycin; tacrolimus; clinical pharmacy

1. Introduction

Therapeutic drug monitoring is a clinical strategy in which measured drug concentrations are integrated with patient characteristics, treatment response, toxicity, pharmacokinetics, and pharmacodynamics to optimize therapy. The principal purpose of TDM is not simply to determine whether a serum concentration lies within a laboratory reference range. Rather, it is to determine whether drug exposure is appropriate for a particular patient and whether the treatment regimen should be changed.

TDM is particularly valuable when a drug has a narrow therapeutic index, substantial pharmacokinetic variability, an established relationship between exposure and efficacy or toxicity, and no readily available clinical marker that can provide sufficiently early assessment of treatment adequacy.

Traditionally monitored medications include vancomycin, aminoglycosides, digoxin, lithium, selected antiseizure medications, immunosuppressants, and several oncology agents. More recently, interest has expanded to beta-lactam antibiotics, biologic agents, targeted anticancer therapies, and other medications for which exposure may vary substantially between patients.

Canada provides an informative example of this transition. Pharmacist-led pharmacokinetic services have existed in Canadian hospitals for decades, but contemporary studies show marked variation in how TDM is performed and how quickly newer exposure-based and Bayesian approaches are being adopted. Canadian experience therefore provides practical insights into both the potential and the implementation challenges of precision dosing.

2. From Therapeutic Range to Individualized Exposure

The conventional approach to TDM often follows a simple sequence:

Administer standard dose → Measure concentration → Compare with therapeutic range → Adjust dose.

Although useful, this approach has limitations.

A concentration cannot be interpreted correctly without considering:

- dose and dosing interval;
- time of administration;
- timing of blood sampling;
- renal and hepatic function;
- body weight and body composition;
- fluid status;
- renal replacement therapy;
- interacting medications;
- disease severity;
- adherence; and
- changes in clearance over time.

A concentration described as “subtherapeutic” may not necessarily require dose escalation, just as a value within a conventional therapeutic range does not guarantee appropriate exposure.

Modern TDM therefore emphasizes the relationship between **dose, concentration, exposure, pharmacodynamic target, and patient outcome**.

Depending on the medication, exposure may be represented by a trough concentration, peak concentration, area under the concentration-time curve (AUC), time above a minimum inhibitory concentration, or another PK/PD parameter.

3. Canada: A Long History of Pharmacist-Led Pharmacokinetic Monitoring

Clinical pharmacists have historically played an important role in Canadian TDM.

A pharmacokinetic service established at Ottawa General Hospital reported comprehensive monitoring of drug concentrations and a 92% acceptance rate for recommendations generated by the clinical pharmacokinetic service. An earlier national survey of Canadian acute-care hospitals also demonstrated pharmacist involvement in pharmacotherapy monitoring and pharmacokinetic services.[1,2]

These historical data are important because the contemporary transition toward precision dosing is not an entirely new clinical service. Rather, MIPD represents an evolution of established pharmacist-led pharmacokinetic practice.

The role has progressed from interpreting measured drug levels to estimating individual pharmacokinetic parameters, predicting future exposure, comparing alternative regimens, and increasingly using computerized models to assist dosage selection.

4. Vancomycin: The Clearest Example of the Transition

Vancomycin illustrates the evolution of TDM particularly well.

Historically, trough concentrations of 15–20 mg/L were frequently used as a surrogate for achieving an AUC-to-MIC ratio associated with efficacy in serious methicillin-resistant *Staphylococcus aureus* infection.

Contemporary consensus guidance instead recommends targeting an AUC₂₄/MIC of approximately 400–600 for serious MRSA infections, primarily to maintain efficacy while reducing excessive exposure and nephrotoxicity.[3]

Canadian vancomycin practice

A cross-sectional survey published in 2023 provides one of the most useful descriptions of TDM practice in Canada. The survey included 120 pharmacists from 10 of Canada's 13 provincial and territorial jurisdictions, representing approximately 12.5% of Canadian acute-care hospitals.[4]

Trough-based monitoring remained dominant:

- **89.9%** reported trough-based monitoring;
- only **10.1%** used AUC-based TDM, either alone or in combination with trough monitoring;
- **80.7%** reported a medical directive allowing pharmacists to order vancomycin concentrations and/or autonomously adjust doses;
- **82.5%** had institution-specific vancomycin TDM guidelines; and
- **61.3%** required specific pharmacist training or credentialing to perform vancomycin TDM.[4]

The geographic pattern was also notable. Of the 12 hospitals reporting AUC-based monitoring, 10 were in Quebec, one in Ontario, and one in Manitoba. Six used publicly available Bayesian software, five used two-sample methods, and one used population pharmacokinetic equations.[4]

These findings demonstrate that pharmacist infrastructure for advanced dosing already exists in Canadian hospitals, but conversion from conventional trough monitoring to exposure-based dosing remains uneven.

5. Canadian Innovation in Bayesian Vancomycin Dosing

Cost is frequently cited as a barrier to implementation of Bayesian software.

Canadian investigators at Lakeridge Health in Ontario developed **VancoCalc**, a free open-source Bayesian vancomycin dosing application. The tool used previously published pharmacokinetic models as priors and was evaluated using data from 52 adult patients and 104 vancomycin concentrations collected at Lakeridge Health.[5]

The median prediction error was -0.60 µg/mL and the median absolute error was 3.05 µg/mL in this preliminary evaluation.[5]

The importance of this work extends beyond the performance of one calculator. It demonstrates a potential strategy for health systems in which proprietary Bayesian platforms may be financially difficult to implement.

However, free software does not eliminate the need for model validation, governance, training, clinical oversight, and appropriate integration into local practice.

6. Aminoglycosides: Persistent Variation in Practice

Aminoglycosides have long represented classic TDM drugs because efficacy and toxicity are strongly related to exposure.

For traditional regimens, peak concentrations provide information related to efficacy, whereas trough concentrations help identify accumulation and toxicity risk. Extended-interval administration uses different pharmacokinetic principles and typically relies on concentration measurements interpreted through a dosing nomogram or individualized PK calculations.

A 2022 survey examining aminoglycoside dosing and monitoring in critically ill patients across Quebec hospitals found that gentamicin and tobramycin dosing was generally consistent with international recommendations, but dose adjustment was frequently based on clinician judgment or locally developed software. The authors identified variability across institutions and suggested a need for greater standardization of aminoglycoside TDM.[6]

This illustrates an important limitation of conventional TDM: measuring drug concentrations does not itself standardize dosing. Interpretation methods, pharmacokinetic assumptions, software, sampling practices, and clinical expertise may still differ significantly between institutions.

7. Expanding TDM to Beta-Lactam Antibiotics

TDM is increasingly being investigated for beta-lactam antibiotics, especially in critically ill patients.

Critical illness can markedly change volume of distribution and renal clearance. Augmented renal clearance may reduce exposure, whereas acute kidney injury or rapidly changing renal function can produce accumulation.

Because beta-lactam efficacy is primarily time dependent, the relevant pharmacodynamic parameter is the proportion of the dosing interval during which unbound concentrations remain above the organism's MIC.

Canadian investigators at the Centre Hospitalier Universitaire de Sherbrooke prospectively evaluated beta-lactam concentrations in 36 critically ill patients with sepsis or septic shock receiving intensive piperacillin-tazobactam or meropenem therapy. All patients achieved concentrations above the MIC throughout the evaluated interval, while 75% achieved concentrations above four times the MIC; 8.3% reached predefined theoretical toxicity thresholds.[7]

The study highlights the potential value of concentration measurement in populations whose pharmacokinetics may be difficult to predict from serum creatinine and conventional dosing categories alone.

Routine beta-lactam TDM nevertheless remains less standardized than monitoring of vancomycin or aminoglycosides, and optimal efficacy and toxicity thresholds require further validation.

8. Immunosuppressants: TDM Beyond Antimicrobials

Tacrolimus represents another major application of individualized pharmacotherapy.

Tacrolimus has a narrow therapeutic index and marked between-patient and within-patient pharmacokinetic variability. Suboptimal exposure may increase the risk of rejection, whereas excessive concentrations can contribute to nephrotoxicity, neurotoxicity, metabolic complications, and other adverse effects.

Canadian practice also illustrates that **more monitoring is not always better**.

At The Ottawa Hospital, tacrolimus concentrations after hematopoietic stem-cell transplantation had historically been measured daily. Following evaluation of local practice, monitoring was changed to daily during the first week and three times weekly thereafter. A subsequent analysis assessed the safety and practicality of this reduced monitoring strategy.[8]

More recently, pharmacists at the Centre Hospitalier de l'Université de Montréal developed a standardized protocol to reduce unnecessary calcineurin-inhibitor monitoring in hospitalized solid-organ transplant recipients. In a 2026 study including **520 hospitalizations**, implementation reduced CNI measurements by approximately **14%**, without significant deterioration in target attainment, dose adjustment, or CNI-related adverse effects.[9]

These findings illustrate an important principle:

Precision monitoring does not necessarily mean more laboratory tests.

The goal is to obtain the right concentration at the right time and use it to make a clinically meaningful decision.

9. Conventional Pharmacokinetics Versus Bayesian Dosing

Traditional individualized pharmacokinetic calculations estimate parameters such as clearance, volume of distribution, elimination rate constant, and half-life from measured concentrations.

These calculations remain clinically useful, particularly when software is unavailable.

However, conventional calculations can become difficult when:

- concentrations are obtained at imperfect times;
- renal function changes rapidly;
- distribution is multicompartmental;
- only one concentration is available;

- patient characteristics differ substantially from standard assumptions; or
- future exposure rather than a single concentration is the therapeutic target.

Bayesian forecasting offers a different approach. The system begins with a population pharmacokinetic model—the **prior**. Patient-specific characteristics and measured drug concentrations are then incorporated to estimate the individual's pharmacokinetic parameters—the **posterior**.

The model can subsequently simulate alternative dosing regimens and estimate which regimen is most likely to achieve the desired exposure.

The process can therefore be summarized as:

Population PK model + patient covariates + measured concentrations → individualized PK estimate → predicted exposure → optimized dose.

10. Model-Informed Precision Dosing

MIPD extends Bayesian TDM by incorporating quantitative models into prospective dosing decisions.

It can use:

- age;
- body weight;
- kidney function;
- genotype;
- disease state;
- laboratory values;
- previous doses;

- drug concentrations;
- concomitant medications; and
- other clinically relevant covariates.

The theoretical advantage is that the clinician no longer waits for repeated inappropriate concentrations before discovering that the standard regimen does not fit the patient.

Instead, available information is continuously used to refine predictions.

Canadian vancomycin research from Université de Montréal and McGill University Health Centre has compared conventional pharmacokinetic equations with Bayesian approaches, contributing to the broader evidence base supporting more sophisticated estimation of vancomycin exposure.[10]

11. Special Populations

The clinical value of individualized dosing becomes particularly apparent in patients whose pharmacokinetics differ substantially from conventional assumptions.

Important populations include:

- critically ill patients;
- neonates and children;
- older adults;
- patients with obesity;
- pregnancy;
- severe burns;
- augmented renal clearance;
- acute kidney injury;
- chronic kidney disease;
- extracorporeal membrane oxygenation;

- intermittent hemodialysis;
- continuous renal replacement therapy; and
- solid-organ or hematopoietic stem-cell transplant recipients.

In these populations, a standard dose may produce markedly different exposure in two apparently similar patients.

MIPD is therefore particularly attractive where the consequences of underexposure or overexposure are clinically important and where pharmacokinetic variability is difficult to capture using fixed dosing algorithms.

12. The Clinical Pharmacist's Role

Canadian evidence repeatedly demonstrates the importance of pharmacists in TDM.

The pharmacist's role extends beyond calculating a dose. It includes:

1. determining whether TDM is clinically indicated;
2. selecting an appropriate sampling strategy;
3. ensuring correct timing and documentation;
4. interpreting concentrations within the clinical context;
5. assessing renal and hepatic function;
6. evaluating drug interactions;
7. estimating pharmacokinetic exposure;
8. recommending or implementing dosage changes;
9. determining when repeat monitoring is necessary;
10. identifying when monitoring can safely be reduced; and
11. evaluating clinical efficacy and toxicity.

The national Canadian vancomycin survey found that pharmacists alone or pharmacists working with physicians were primarily responsible for TDM in more than half of participating institutions, while most hospitals permitted pharmacists to order levels and/or adjust therapy under medical directives.[4]

This existing clinical infrastructure provides a strong foundation for future implementation of MIPD.

13. Barriers to Model-Informed Precision Dosing in Canada

Canadian experience also demonstrates why adoption cannot be driven by guidelines alone. Hospitals considering AUC-based vancomycin monitoring identified several anticipated barriers, including lack of physician familiarity, need for staff training, additional blood concentrations, laboratory and nursing resources, pharmacist time, specimen-timing problems, software cost, and risk of implementation errors.[4]

Interestingly, institutions already using AUC-based methods perceived several of these barriers as less problematic than hospitals that had not yet implemented them.[4]

Successful implementation therefore requires a health-system approach involving:

- validated pharmacokinetic models;
- laboratory capability;
- electronic medication administration data;
- accurate sampling documentation;
- clinical pharmacist expertise;
- physician engagement;
- nursing education;
- information technology support;
- software governance;
- institutional protocols; and
- quality-assurance monitoring.

14. From Drug Level to Clinical Decision

One of the most important changes in modern TDM is conceptual.

A laboratory concentration should not be treated as the endpoint.

The clinically relevant sequence is:

Patient → Drug → Dose → Concentration → Exposure → Effect → Clinical decision.

A drug concentration has value only when it changes the probability of making a better therapeutic decision.

This principle also prevents unnecessary testing. Routine concentrations should not be ordered simply because a medication historically appears on a TDM list.

Monitoring should answer a specific clinical question.

15. Future Directions

The next phase of precision dosing will likely combine pharmacokinetic models with automated data extraction from electronic health records.

Potential developments include:

- automatic import of medication administration times;
- automated laboratory data integration;
- real-time renal-function updates;
- Bayesian forecasting;
- automated identification of patients requiring TDM;
- concentration-sampling recommendations;
- dose simulation;

- pharmacogenomic information;
- clinical decision support; and
- artificial-intelligence-assisted prioritization.

However, automation must not remove clinical oversight.

Models can estimate exposure but cannot independently determine whether the diagnosis is correct, whether therapy remains necessary, whether source control has been achieved, or whether treatment goals have changed.

The appropriate future model is therefore:

automation of calculation + preservation of clinical judgment.

16. Conclusion

Therapeutic drug monitoring is evolving from conventional concentration-based monitoring toward individualized exposure-guided pharmacotherapy.

Canadian practice provides a useful illustration of this transition. Pharmacist-led pharmacokinetic services have a long history in Canadian hospitals, and contemporary data demonstrate extensive pharmacist responsibility for vancomycin monitoring. At the same time, national and provincial studies reveal substantial variability in the implementation of AUC-guided vancomycin monitoring, aminoglycoside dosing, and other TDM practices.

Canadian research has also contributed to open-source Bayesian vancomycin dosing, beta-lactam concentration monitoring in critically ill patients, and optimization of tacrolimus and calcineurin-inhibitor monitoring.

The future of TDM should therefore not be defined by obtaining more drug levels. It should be defined by obtaining **better information and converting that information into better individualized dosing decisions.**

The progression can be summarized as:

Therapeutic range → Pharmacokinetic interpretation → Exposure targeting → Bayesian forecasting → Model-informed precision dosing.

For clinical pharmacists, this evolution represents a natural extension of traditional pharmacokinetic expertise and an important opportunity to advance individualized medication therapy.

Ethics & Declarations

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable. This study did not involve human participants, animal experimentation, or confidential patient clinical data.

Consent for Publication

Not applicable, or informed consent for publication was obtained from all individual participants where relevant.

Competing Interests

The authors declare that they have no competing financial or non-financial interests.

Funding

The authors declare that no funds, grants, or other financial support were received during the preparation of this manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during the current study.

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