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Resolving Medication Reconciliation

Robert MacLaren

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Intrinsic to the medication reconciliation process are three steps: (1) verification or gathering the best possible medication history, (2) clarification or ensuring the appropriateness of the medication and dosage regimen, and (3) resolution or resolving discrepancies.[1] While the purpose of reconciliation is to avoid medication errors, the ultimate goals are to improve patient safety and reduce clinical complications associated with medication errors. So important is medication reconciliation that the World Health Organization developed a standard implementation protocol to aid in its application.[1]

In this issue are two intriguing studies that highlight the importance of medication reconciliation but also generate questions.[2,3] In one of these studies, Sanh and others[2] investigated elderly patients with high health care utilization at two academic hospitals and found that potentially inappropriate prescribing occurred in 89% of patients, with both potentially inappropriate medications and potential prescribing omissions being common. The therapeutic classes of medications most often implicated included anticoagulants and antiplatelet agents, renin-angiotensin-aldosterone system (RAAS) inhibitors, benzodiazepines, and opioids. Of note, only 14% of the cases of potentially inappropriate prescribing had been addressed by the time of hospital discharge. The other study was conducted by Abu Hammour and others.[3] After initial screening for unintentional medication discrepancies, 123 surgical patients were randomly assigned to receive medication reconciliation or standard care. Although the number of discrepancies per patient tended to be higher at baseline in the medication reconciliation group, the reduction in discrepancies at discharge was similar between groups. Of clinical importance is that a total of 46 discrepancies were potentially moderately to severely harmful.

Medication reconciliation is resource intensive and often complicated by workflow challenges and system complexities. The results of these two studies highlight that potentially inappropriate prescribing is common among hospitalized patients and that pharmacists are ideally situated to identify such problems. These data are consistent with most other studies.[4] What might surprise readers is the lack of resolution of discrepancies in the two highlighted studies, especially considering that the implicated therapeutic classes were high-risk medications or represented potentially harmful outcomes. In general, however, the literature lacks information about beneficial safety and clinical outcomes associated with medication reconciliation.[4] As a result, practitioners face the challenge of determining whether medication reconciliation is cost effective.

Inconsistent approaches to resolution may explain the lack of demonstrable clinical benefit with medication reconciliation. A recent randomized, multicentre investigation of 1499 patients showed that medication reconciliation by a pharmacist, combined with motivational interviewing and long-term provider interactions, reduced readmission rates at 30 and 180 days, whereas basic medication review had no impact.[5] Similarly, in a systematic review of 17 studies, medication reconciliation that included telephone follow-up or home visits and patient counselling reduced emergency visits and hospital readmissions.[6] In other words, medication reconciliation improved outcomes only when a process for resolution was evident. The obvious critique of these data is the intensive services that were needed to optimize resolution. However, the results suggest that identifying best practices for the process of resolution is imperative if the goals of medication reconciliation are to improve safety and clinical outcomes. Pharmacists are integral to medication reconciliation, and evidence supports their involvement in the steps of verification and clarification. What is needed now is additional investigation about the optimal role of the pharmacist in the resolution step.

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ON THE FRONT COVER

Hoodoos, Drumheller, Alberta

This photograph was taken by Scot Simpson during a family trip to Drumheller, Alberta. He and his family enjoyed seeing dinosaurs at the Royal Tyrrell Museum, a tipple at the Atlas Coal Mine, and these hoodoos. Scot captured this image using a Nikon D3200 Digital SLR with 18–55 mm lens set to ISO 100, 1/640 exposure, f/3.8.

Scot is a professor in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta. He is a pharmacoepidemiologist and health services researcher with an interest in diabetes management. When not working, he can be found out on the Edmonton River valley trails with his dog or on his mountain bike.

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La résolution du bilan comparatif des médicaments

par Robert MacLaren

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Le processus du bilan comparatif des médicaments comprend trois étapes intrinsèques : 1) la vérification ou la collecte des meilleurs antécédents médicamenteux possibles; 2) la clarification ou l'assurance de la pertinence de la médication et de la posologie; et 3) la résolution des divergences.[1] Bien que l'objectif du bilan consiste à éviter les erreurs de médication, les buts ultimes consistent, eux, à améliorer la sécurité des patients et à réduire les complications cliniques associées aux erreurs de médication. Le bilan comparatif des médicaments est si important que l'Organisation mondiale de la Santé a élaboré un protocole de mise en œuvre standard pour faciliter son application.[1]

Dans ce numéro, deux études intrigantes soulignent l'importance du bilan comparatif des médicaments, mais suscitent également des questions.[2,3] Dans l'une d'elles, Sanh *et al.*[2] ont enquêté dans deux hôpitaux universitaires sur des patients âgés ayant une utilisation élevée de soins de santé et ont constaté que des prescriptions potentiellement inappropriées se produisaient chez 89 % des patients – les médicaments potentiellement inappropriés et les omissions potentielles de prescription étant courants. Les classes thérapeutiques de médicaments le plus souvent en cause étaient les anticoagulants et les antiagrégants plaquettaires, les inhibiteurs du système rénine-angiotensine-aldostérone (SRAA), les benzodiazépines et les opioïdes. Il convient de noter que seulement 14 % des cas de prescription potentiellement inappropriée avaient été traités au moment de la sortie de l'hôpital. L'autre étude a été menée par Abu Hammour *et al.*[3] Après le dépistage initial des divergences médicamenteuses non intentionnelles, 123 patients chirurgicaux ont reçu soit un bilan comparatif des médicaments ou des soins standard, selon une répartition aléatoire. Bien que le nombre d'écarts par patient avait tendance à être plus élevé au départ dans le groupe du bilan comparatif des médicaments, la réduction des écarts au moment de la sortie de l'hôpital était similaire entre les groupes. Ce qui est important sur le plan clinique, c'est qu'un total de 46 écarts étaient potentiellement de modérément à gravement nocifs.

Le bilan comparatif des médicaments nécessite beaucoup de ressources et est souvent rendu difficile par les problèmes sur les plans du flux de travail et de la complexité du système. Les résultats de ces deux études soulignent que la prescription potentiellement inappropriée est fréquente chez les patients hospitalisés et que les pharmaciens sont bien placés pour identifier de tels problèmes. Ces données cadrent avec la plupart des autres études.[4] Ce qui pourrait surprendre le lecteur, par contre, c'est le manque de résolution des divergences dans les deux études mises en évidence, d'autant plus que les classes thérapeutiques en question étaient des médicaments à haut risque ou représentaient des résultats potentiellement nocifs. En général, cependant, la littérature manque d'informations sur l'innocuité bénéfique et les résultats cliniques associés au bilan comparatif des médicaments.[4] Par conséquent, les praticiens doivent relever le défi visant à déterminer si le bilan est rentable.

Un manque d'uniformité dans les démarches utilisées pour la résolution peut expliquer l'absence de bénéfice clinique ayant fait ses preuves du bilan comparatif des médicaments. Une récente enquête randomisée multicentrique portant sur 1499 patients a démontré que le bilan comparatif des médicaments exécuté par un pharmacien, combiné à des entretiens motivationnels et à des interactions à long terme avec les prestataires, réduisait les taux de réadmission à 30 et 180 jours, alors que la révision de base des médicaments n'avait aucun impact.[5] De même, dans une revue systématique de 17 études, un bilan comparatif des médicaments qui comprenait un suivi téléphonique ou des visites à domicile et des conseils aux patients a réduit les visites aux urgences et les réadmissions à l'hôpital.[6] En d'autres termes, le bilan comparatif des médicaments n'améliorait les résultats que lorsqu'un processus de résolution était évident. La critique évidente qui ressort de ces données est la quantité de services intensifs qui ont été nécessaires pour optimiser la résolution. Cependant, les résultats indiqueraient que l'identification des meilleures pratiques pour le processus de résolution est impérative si les objectifs du bilan comparatif des médicaments visent à améliorer la sécurité et les résultats cliniques. Les pharmaciens font partie intégrante du bilan comparatif des médicaments, et les preuves appuient leur implication dans les étapes de

vérification et de clarification. Ce qu'il faut maintenant, c'est une enquête supplémentaire sur le rôle optimal du pharmacien à l'étape de la résolution.

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Application of Failure Mode, Effects, and Criticality Analysis to the Medication-Use Process for Temperature-Sensitive Drugs in a University Hospital

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ABSTRACT

Background: In the hospital setting, the medication-use system for temperature-sensitive drugs is a high-risk process.

Objectives: To analyze the risks associated with the hospital-based medication-use process and to propose corrective and preventive actions for the most critical failure modes.

Methods: A multidisciplinary team was trained to analyze the medication-use process for temperature-sensitive drugs and to identify potential failures using a risk analysis method known as failure mode, effects, and criticality analysis (FMECA). The medication-use process, from initial supply to administration to patients, was investigated using "the 5 Ws and How" method (Who? What? Where? When? Why? How?), and the causes of the failure modes were analyzed using Ishikawa diagrams. The most critical failure modes were selected using the Pareto law, and relevant improvement actions were proposed.

Results: This analysis identified 41 failure modes for the 9 stages of the medication-use process, of which only 36 were deemed assessable by the participants. Eighteen (50%) of these failure modes were critical, according to the Pareto law, with criticality indices between 12 and 60. The stage of tidying up and storage in patient care units had the highest number of critical failures ($n = 5$). A total of 48 corrective actions were proposed.

Conclusion: The proposed action plan prioritized 3 areas for improvement: the documentation system, staff training, and equipment acquisition. A second FMECA should be carried out to reassess the medication-use process after implementation of these improvement actions. The second FMECA, allowing detection of residual risks and identification of new risks, will be part of a continuous improvement process.

Keywords: cold chain, temperature-sensitive drug, risk management, patient safety

RÉSUMÉ

Contexte : Le circuit des médicaments thermosensibles en milieu hospitalier fait partie des processus à risque.

Objectifs : Analyser a priori les risques liés à ce circuit et proposer des actions correctives et préventives contre les modes de défaillances les plus critiques.

Méthodes : Une équipe pluridisciplinaire a été formée pour analyser le circuit des médicaments thermosensibles et identifier les défaillances par la méthode de l'analyse des modes de défaillances, de leurs effets et de leurs criticités (AMDEC). Le processus, qui va de l'approvisionnement jusqu'à l'administration des médicaments aux patients, a été décortiqué en utilisant la méthode « Qui? Quoi? Où? Quand? Comment? Pourquoi? » (QQOQCP) et les causes des défaillances ont été analysées à l'aide de diagrammes d'Ishikawa. Les défaillances les plus critiques ont été sélectionnées par la loi de Pareto, et des mesures d'amélioration pertinentes ont été proposées.

Résultats : Cette analyse a mis en évidence 41 modes de défaillances pour les 9 étapes du circuit, dont uniquement 36 sont jugés évaluables par les membres de l'équipe pluridisciplinaire. Dix-huit modes sur 36 (soit 50 %) sont critiques selon la loi de Pareto, avec des indices de criticité répartis entre 12 et 60. L'étape comprenant le nombre le plus élevé de défaillances critiques est celle du rangement et du stockage dans les services de soins, avec 5 défaillances. Au total, 48 mesures correctives ont été proposées.

Conclusions : Le plan d'action proposé priorisait 3 domaines d'amélioration : le système de documentation, la formation du personnel et l'acquisition d'équipements. Une deuxième AMDEC devrait être réalisée pour réévaluer le circuit après la mise en œuvre des mesures d'amélioration. La deuxième AMDEC permettra la détection des risques résiduels et l'identification de nouveaux risques et s'inscrira dans une démarche d'amélioration continue.

Mots-clés : chaîne du froid, médicament thermosensible, gestion des risques, sécurité des patients

INTRODUCTION

The cold chain is the set of logistic links that guarantee maintenance of a temperature between 2°C and 8°C during the stages of storage, handling, transport, and distribution of drugs. Any improper operation in the process of cold chain logistics may have a significant effect on the quality of temperature-sensitive drugs and vaccines, endangering the safety of patients receiving them. For example, power outages, inadequate conditions during transport, or unsuitable storage conditions can lead to a break in the cold chain, causing the degradation of vaccines and other pharmaceuticals.[1,2] In fact, a drug's properties may change with any temperature variation, depending on the temperature reached and the duration of storage at that temperature.[1,3] Certain drugs may lose some clinical effectiveness, whereas others may have a complete loss of activity or may even become toxic.[1,4,5] Thus, the cold chain is a major concern for hospitals, both financially and in terms of patient safety. Managing the operation of the cold chain, defining its players, ensuring its performance, and securing the medication-use process for temperature-sensitive drugs must therefore be included among the hospital's priorities, especially for the pharmacy department. Indeed, the hospital pharmacist represents an essential link in the cold chain, intervening in almost all stages of the system, from purchase and supply to administration to patients. Errors may occur at any stage of the process, with the pharmacist being responsible not only for identifying the failures but also for evaluating them and implementing the measures necessary to correct or prevent them.[6,7]

The objectives of this study were to analyze a priori the potential failure modes of the medication-use process for temperature-sensitive drugs and to propose corrective and preventive actions, by setting up a concrete action plan to minimize the risks and ensure the safety of the system and thus the safety of patients.

METHODS

Study Design and Setting

This study was a failure mode, effects, and criticality analysis (FMECA), carried out in the pharmacy department of a university hospital over a 3-month period (October to December 2019). The FMECA involved 6 steps: training, functional analysis, qualitative study, quantitative study, determination of the hierarchy of criticality, and proposals for improvement.[8-10]

Step 1: Training the Team

A multidisciplinary working group was trained to ensure consistency in the discussion and rating of failure modes. The group was made up of 8 members: 2 pharmacists (H.S., K.B.J.), 1 doctor, 3 pharmacy interns (including I.C.), 1 nurse, and 1 pharmacy assistant. For implementation of the study, 4 bimonthly meetings were scheduled.

Step 2: Functional Analysis: Description of Process

The working group described the medication-use process for temperature-sensitive drugs, from supply to administration, using the "5 Ws and How" method (Who? What? Where? When? Why? How?). This method allowed us to analyze the various stages, to define the main actors at each stage, and to describe the medication-use process clearly and simply.

Step 3: Qualitative Study: Risk Analysis of the Process

The working group identified potential failure modes by brainstorming. For each failure mode, the possible effects on or consequences for both the patient and the temperature-sensitive drugs were defined, the causes of failure were identified, and various means of detecting the risk were found. The causes were analyzed using Ishikawa ("fishbone") diagrams showing the following 5 aspects: personnel (man/labour), machinery (equipment, technology), material (raw materials, consumables, and information), method (process), and measurement or environment.

For each stage of the medication-use process, a summary matrix of failure modes, as well as their causes and effects, was developed.

Step 4: Quantitative Study: Quantification of Risks

The same matrix was used for rating the frequencies, detectability, and severity of failure modes according to proposed scales (Table 1). Decisions were based on voting by the working group, with divergent ratings subject to discussion to ensure consensus.

Step 5: Hierarchy of Criticality Determined by the Pareto Law

The criticality index of each failure mode was calculated as the product of frequency, detectability, and severity. This calculation made it possible to prioritize the various failure modes identified and to appropriately target actions to be taken.

For this purpose, the working group used a Pareto diagram. This type of diagram is based on the empirical law of 80/20, whereby about 20% of causes explain up to 80% of a problem. In this case, 20% of the failure modes were assumed to account for 80% of the criticality index.

After ranking the failure modes in descending order according to their respective criticality indexes, the cumulative criticality indexes and the percentages of cumulative criticality indexes were calculated for application of the Pareto law.

Step 6: Proposal of Improvement Actions

Once the most critical failure modes were identified, corrective action plans were put into place.

RESULTS

Functional Analysis: Description of Process

Figure 1 shows an excerpt of the medication-use process for temperature-sensitive drugs, as described by the "5 Ws and How" method.

Qualitative Study: Risk Analysis

A total of 41 failure modes were identified and subjected to analysis. The highest number of failure modes was recorded for storage stages at the storehouse, in pharmacy units, and in patient care units (n = 9 failure modes for each location). The lowest number of failures (n = 1) was found for the stage of order reception at the storehouse.

The working group deemed 5 failures to be non-evaluable, because they were not specific to the medication-use process for temperature-sensitive drugs. Three of these failure modes belonged to the first stage, relating to purchase and supply (error in supply of the product, delay in supply of the product, insufficient amount ordered relative to need); one occurred in the second stage, relating to delivery and transport (delivery error); and one occurred in the seventh stage, relating to dispensing to care units (error in dispensing). In the end, 36 failure modes were selected for evaluation (Table 2).

As an example, Figure 2 shows an Ishikawa ("fishbone") diagram for the failure mode of a power outage.

Quantitative Study

Criticality indexes were calculated for the failure modes identified in the qualitative study. The calculated values were between 4 and 60, as shown in Table 2.

TABLE 1. Scales Considered for Scoring Failure Modes

Scale Designation	Description
Severity (S) of effects	
S1	No impact on the drug (drug stable, packaging intact)
S2	Alteration of packaging, with no effect on the drug
S3	Decrease in duration of stability of the active substance (alteration of active substance)
S4	Degradation of active substance; drug not administered to patients
S5	Degradation of active substance; safety or therapeutic effectiveness compromised in the event of administration to patients
Frequency (F) of occurrence	
F1	Exceptional, no record of occurrence or virtually nonexistent
F2	Rare (1 or 2 times per year)
F3	Frequent (several times per year)
F4	Certain to occur (always)
Detectability (D)	
D1	High: probability is high that failure mode will be detected before it reaches the patient
D2	Possible: failure mode can be detected, but there is a risk of it being overlooked
D3	Unlikely: detection of failure mode is difficult
D4	Impossible: failure mode cannot be detected

Stage n° 1: Purchase and supply					
What?	**Who?**	**Where?**	**When?**	**How?**	**Why?**
• Supply of drugs	• The pharmacist responsible for the supply	• Pharmacy depot	• Before the stock runs out • At the request of doctors	• By establishing a purchase order	• To avoid out of stock • To meet the needs of the hospital • To provide treatment to patients
Stage n° 2: Delivery and transport of TSD					
What?	**Who?**	**Where?**	**When?**	**How?**	**Why?**
• To transport the order to the pharmacy depot	• Agent responsible for transport	• Drug transport truck in coolers	• Following the delivery of the order by the supplier	• By respecting the cold chain and transport conditions using coolers	• To supply the hospital when needed without any delay

FIGURE 1. Excerpt from description of the medication-use process for temperature-sensitive drugs (TSDs), according to the "5 Ws and How" method.

TABLE 2 (Part 1 of 2). Rating of Failure Modes and Calculation of Criticality Indices

Stage	Designation	Failure Mode	Severity	Frequency	Detectability	Criticality Index[a]
Delivery and transport	FM1	Noncompliance with cold chain during transport	4	3	2	24
Receipt of order at storehouse	FM2	No temperature control in reception area	5	3	2	30
Storage at storehouse	FM3	Medicines left outside refrigerated cabinet before storage	4	1	1	4
	FM4	Power outage	4	3	2	24
	FM5	Refrigerated cabinet failure	4	1	1	4
	FM6	Door of refrigerated cabinet not closed properly	4	2	1	8
	FM7	Prolonged or frequent opening of door to refrigerated cabinet	1	3	2	6
	FM8	Required temperature not reached in refrigerated cabinet	4	1	1	4
	FM9	Storage of boxes in unsuitable space in storehouse	3	4	1	12
	FM10	Refrigerated cabinets cluttered with medication	2	3	1	6
	FM11	Difference between temperature showing on refrigerated cabinet display and actual temperature	5	2	3	30
Distribution from storehouse to pharmacy units	FM12	Advance preparation of orders for temperature-sensitive drugs	4	1	2	8
	FM13	Noncompliance with cold chain during transport to pharmacy units	4	3	3	36
	FM14	No monitoring of compliance with cold chain in the reception area	5	4	1	20
Storage in the various pharmacy units	FM15	Power outage	4	3	2	24
	FM16	Difference between temperature displayed on thermometer and actual temperature	5	2	3	30
	FM17	Refrigerator failure	4	1	1	4
	FM18	Refrigerator door not closed properly	4	3	1	12
	FM19	Required temperature not reached in refrigerator	4	2	1	8
	FM20	Prolonged or frequent opening of refrigerator door	1	3	2	6
	FM21	Inadequate storage in refrigerator (in vegetable drawer or in door or in contact with freezer compartment or frozen walls of refrigerator)	5	1	1	5
	FM22	Storage of boxes in an unsuitable space within pharmacy unit	3	2	1	6
	FM23	Refrigerators cluttered with medication	3	2	1	6
Dispensing from pharmacy to the various care units	FM24	Advance preparation of orders for temperature-sensitive drugs	5	1	3	15
	FM25	Noncompliance with cold chain during transport to care units	5	4	1	20
Storage in patient care units	FM26	Medication left outside refrigerator before storage	5	3	2	30
	FM27	Power outage	5	2	1	10
	FM28	Refrigerator failure	4	2	1	8
	FM29	Refrigerator door not closed properly	5	3	1	15
	FM30	Required temperature not reached in refrigerator	5	2	4	40
	FM31	Prolonged or frequent opening of refrigerator door	1	3	2	6
	FM32	Inadequate storage in refrigerator (in vegetable drawer or in door or in contact with freezer compartment or frozen walls of the refrigerator)	5	4	1	20
	FM33	Difference between temperature displayed on thermometer and actual temperature	5	3	4	60
	FM34	Storage of temperature-sensitive drugs outside refrigerator (in the cabinet)	5	1	1	5

TABLE 2 (Part 2 of 2). Rating of Failure Modes and Calculation of Criticality Indices

Stage	Designation	Failure Mode	Severity	Frequency	Detectability	Criticality Index[a]
Administration to patients	FM35	Extended interval between taking medicine out of the refrigerator and administering it to patient	5	2	2	20
	FM36	Error in preparation of temperature-sensitive injectable drugs: injection without prior warming	1	2	4	8

FM = failure mode.
[a]Criticality index was calculated as the product of severity × frequency × detectability.

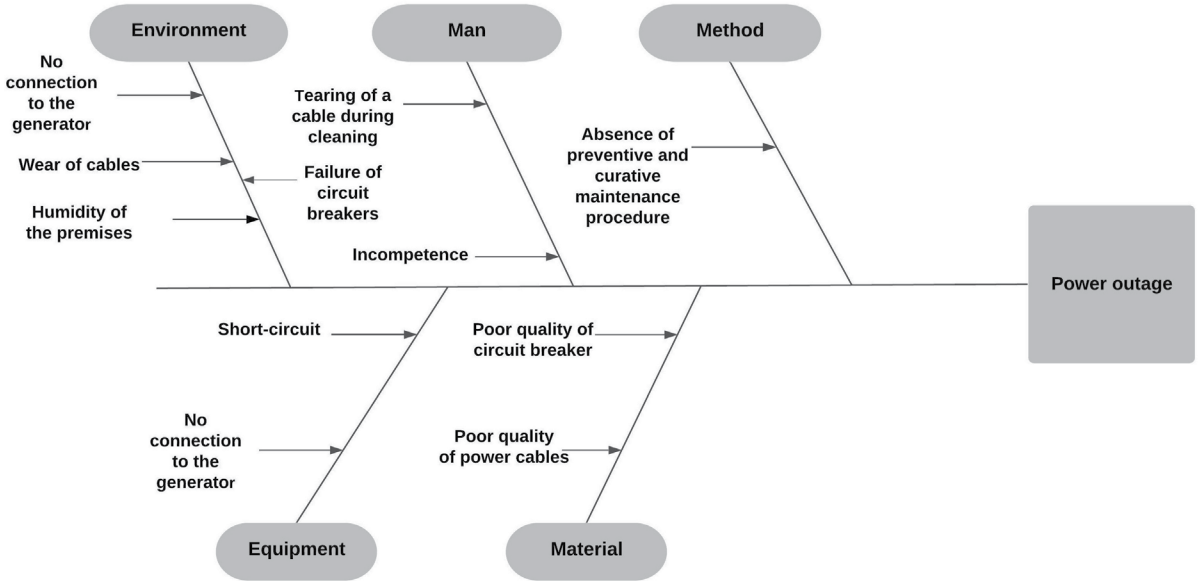

FIGURE 2. Example of an Ishikawa ("fishbone") diagram for the failure mode of a power outage.

Hierarchy of Failures: Pareto Law

According to the Pareto law, 18 of the 36 failure modes were critical, having criticality indexes between 12 and 60. Figure 3 illustrates the Pareto chart.

Most of the critical failures (n = 11) were related to the storage stages: in patient care units (n = 5), in the storehouse (n = 3), and in the pharmacy units (n = 3).

Improvement Actions

According to the most critical failure modes selected by the Pareto law, the working group proposed several ameliorative, corrective, and preventive actions. These actions will be implemented gradually over time, with deadlines for action in the long, medium, and short terms, according to the hospital's financial resources (Table 3).

Monitoring indicators were put in place to measure the impact of these improvement actions. The first indicator chosen by the working group was the number of temperature alerts, an indirect measure of the efficacy and safety of temperature-sensitive drugs. The second monitoring indicator was the state of operation of cold chain equipment, to identify maintenance needs, with the goal of preserving the quality of temperature-sensitive drugs. This indicator is used for operational purposes (i.e., updating the maintenance plan).

DISCUSSION

Controlling the cold chain remains a topical issue for hospitals. It is linked to a triple risk: a financial or economic risk, a regulatory risk, and above all a risk to patients if the quality of a drug is altered.[11] As intervenors in the cold chain, pharmacists play an important role in preserving the integrity and safety of each drug.[12]

In this study, the a priori analysis of risks associated with the medication-use process for temperature-sensitive drugs was carried out by the FMECA method because it is the most suitable method for the hospital setting, according to several previous studies.[9,13-15] It has been recommended by the French Haute Autorité de Santé (National Authority for Health)[16] as a reference method for risk analysis and has been recommended by several other health organizations, in particular the Institute for Healthcare Improvement,[17] the Institute for Safe Medication Practices Canada,[18] and the American Association of Physicists in Medicine.[19]

The FMECA method is based on the concept of brainstorming. This method of combining ideas is 1 of the 7 basic tools of quality.[20] It is a creative technique that allows the emergence of new ideas in groups.[21] The CHU Sainte-Justine in Montréal, Quebec, applied this technique in the search for failure modes for an evaluation of the various stages of drug administration.[22] The major strengths of FMECA are its simplicity and the quantitative evaluation it allows through a combination of 3 parameters: frequency, severity, and detectability. Moreover, the FMECA helps in identifying the most important critical events, which is helpful for deciding upon and prioritizing improvement actions.[22] However, the FMECA methodology does not specify the procedure to be followed for prioritization. In the AMELIORE study, the team opted for a criticality threshold beyond which recommendations were made[23]; however, they did not explain their choice of threshold value. Arenas Villafranca and others[24] classified failure modes according to their relative importance. They subsequently developed a checklist to determine the "most critical aspects of the process". Again, however, the method of selecting priority risks was not specified. In the current study, the Pareto law was used to define critical failure modes. This choice was approved by all participants, given the method's advantages, including time savings. The criticality index can be rated according to a scale that allows visual assessment using a colour code: green for acceptable, yellow for tolerable, and red for unacceptable.[25] In other studies,[9,14] the criticality index was positioned in a matrix developed by the working group. It can be divided into 3 or more levels, for example, acceptable, tolerable, and unacceptable risk or, alternatively, low, high, and major criticality. Improvement actions are then prioritized according to these categories.

The Pareto law allowed us to select 18 critical failure modes. The stage with the most failure modes was storage in patient care units. Conversely, the stages of delivery and transport and of receipt of the order at the storehouse had the least critical failure modes.

These results cannot be directly compared with any study in the literature because we found no prior studies using FMECA to analyze the medication-use process for temperature-sensitive drugs. Instead, we compared our results with those of studies using the FMECA method and studies on improvement of the cold chain. One study of the latter type, conducted in a health care establishment, highlighted 14 critical points along the entire medication-use process for temperature-sensitive drugs, beginning with delivery by suppliers and ending with delivery to patients[11]; by comparison, we found 18 points of critical failure. Some failure modes were common to the earlier cold chain study[11] and our analysis, namely, noncompliance with the cold chain during transport from the supplier, absence of temperature indicators in the medication packages, noncompliance of pharmacy refrigerators and cold rooms, noncompliance with the cold chain during transport to clinical departments, and storage conditions for products requiring temperature control in compliant refrigerators in clinical departments. Indeed, the delivery and transport stage in our study showed a single critical failure with a criticality index of 24, suggesting noncompliance with the cold chain during transport. This crucial stage must be appropriately controlled, given it is the first link in the entire cold chain. The study by Saint-Lorant and others[11] similarly showed that the transport stage is critical. The only efficient way to transport temperature-sensitive drugs is to use a refrigerated truck, to equip the packages with a USB temperature recorder, and to train logistics staff. The stage of order reception at the

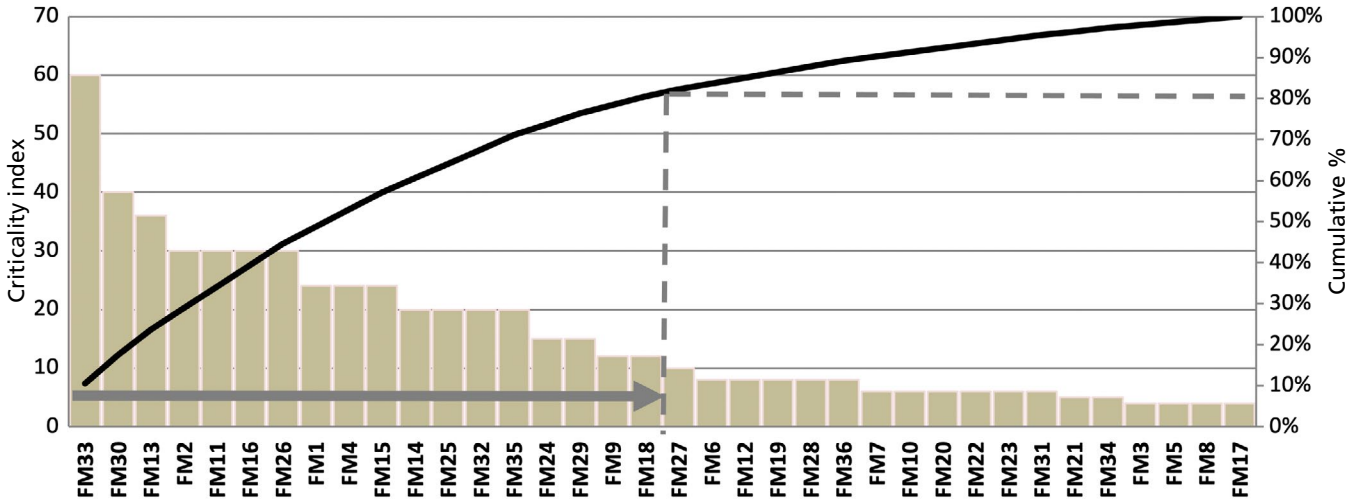

FIGURE 3. Pareto chart. The failure modes (FMs) are presented along the horizontal axis in descending order of their criticality index. The solid black curve depicts the cumulative percentage of the criticality index. The point along the horizontal axis intersecting the 80% value on the right-hand vertical axis (as shown by dashed grey lines) defines the failure modes that were deemed to be critical (spanned by the horizontal grey arrow).

TABLE 3 (Part 1 of 2). Critical Failure Modes Selected by Pareto Law and Proposed Improvement Actions[a]

Designation	Failure Mode	Stage	Criticality Index		Actions	Time Frame
			Value	Cumulative %		
FM33	Difference between temperature displayed on thermometer and actual temperature	Storage in patient care units	60	10	Set up a preventive maintenance procedure for refrigerators Calibrate the thermometer Train and sensitize paramedical staff Establish a standard sheet for daily temperature monitoring (3 times/day)	Short term Long term Short term Short term
FM30	Required temperature not reached in refrigerator	Storage in patient care units	40	17	Set up a preventive maintenance procedure for refrigerators	Short term
FM13	Noncompliance with cold chain during transport to pharmacy units	Distribution from storehouse to pharmacy units	36	24	Train paramedical staff Draft procedures Put in place suitable packaging and isothermal bags for transport Install thermometers in packages	Short term Short term Medium term Medium term
FM2	No temperature control in reception area	Receipt of order at storehouse	30	29	Place the USB temperature recorder inside the package from the time of order delivery to allow visualization of the temperature variation curve Train storehouse staff Set up a procedure to organize the receipt of temperature-sensitive drugs	Medium term Medium term Short term
FM11	Difference between temperature showing on refrigerated cabinet display and actual temperature	Storage at storehouse	30	34	Set up a preventive maintenance procedure for refrigerated cabinets Qualify refrigerated cabinets	Short term Long term
FM16	Difference between temperature displayed on thermometer and actual temperature	Storage in the various pharmacy units	30	39	Establish a preventive maintenance schedule Calibrate thermometers	Medium term Long term
FM26	Medication left outside refrigerator before storage	Storage in patient care units	30	45	Designate an agent responsible for collecting the order and putting it away Raise awareness and train paramedical staff on the importance of respecting the cold chain Develop a procedure for receipt of temperature-sensitive drugs in patient care units	Short term
FM1	Noncompliance with cold chain during transport	Delivery and transport	24	49	Plan the departure time of the truck according to traffic conditions, and choose the shortest route possible Assign the truck driver only one task (to collect the order of the temperature-sensitive drugs) Acquire a refrigerated truck and a USB temperature recorder Train and sensitize the driver Develop a procedure to organize the transport stage of temperature-sensitive drugs	Short term Short term Medium term Short term Short term

TABLE 3 (Part 2 of 2). Critical Failure Modes Selected by Pareto Law and Proposed Improvement Actions[a]

Designation	Failure Mode	Stage	Criticality Index		Actions	Time Frame
			Value	Cumulative %		
FM4	Power outage	Storage at storehouse	24	53	Install an audible alarm system Establish a preventive maintenance schedule Train staff Implement a procedure in case of a break in the cold chain Install a preventive system for activation during natural disasters	Long term Long term Short term Short term Long term
FM15	Power outage	Storage in the various pharmacy units	24	57	Install an audible alarm system Connect the power generator Ensure regular maintenance of the electrical installation	Long term Short term Medium term
FM14	No monitoring of compliance with cold chain in reception area	Distribution to pharmacy units from storehouse	20	61	Equip packages with calibrated thermometers Set up a procedure to organize the receipt of temperature-sensitive drugs	Medium term Short term
FM25	Noncompliance with cold chain during transport to care units	Dispensing from pharmacy to the various care units	20	64	Acquire coolers or isothermal packets for delivery to clinical services Equip packages with calibrated thermometers	Medium term
FM32	Inadequate storage in refrigerator (in vegetable drawer or in door or in contact with freezer compartment or frozen walls of refrigerator)	Storage in patient care units	20	68	Train paramedical staff on rules for storage Perform pharmaceutical audits in clinical departments	Short term
FM35	Extended interval between taking medicine out of refrigerator and administering it to patient	Administration to patients	20	71	Inform and train paramedical staff on rules for using temperature-sensitive drugs Distribute tasks within the service for better organization	Short term
FM24	Advance preparation of orders for temperature-sensitive drugs	Dispensing from the pharmacy to the various care units	15	74	Take temperature-sensitive drugs out of refrigerated storate at the last minute before they are dispensed Train staff	Short term
FM29	Refrigerator door not closed properly	Storage in patient care units	15	76	Train staff Ensure regular maintenance of equipment	Short term Medium term
FM9	Storage of boxes in an unsuitable space	Storage at storehouse	12	78	Empty boxes of temperature-sensitive drugs and transfer to refrigerated cabinet upon receipt Organize the frequency of orders for temperature-sensitive drugs as needed	Short term
FM18	Refrigerator door not closed properly	Storage in various pharmacy units	12	80	Train staff Ensure regular maintenance of equipment	Short term Medium term

FM = failure mode.
[a]Rows are presented in descending order.

pharmacy storehouse also had a single failure (lack of temperature control in the reception area), which was deemed to be critical, according to the 80/20 law. To secure this stage, it is important to check the USB temperature recorder of the order upon receipt, to prioritize documentation of receipt of temperature-sensitive drugs, and to put them away promptly. Saint-Lorant and others[11] suggested limiting the number of people involved in accepting medication deliveries and to make the receptionist aware of the importance of this task.

Eleven of the 18 critical failure modes identified in the current study involved storage: at the storehouse, in the various pharmacy units, and in patient care units. Three failure modes related to storage in the storehouse were deemed critical. The first was a difference between the temperature shown on the display and the actual temperature. To remedy this potential failure mode, the working group proposed qualifying the refrigerated cabinets, to verify that the device continued to operate well under actual conditions of use over time (monitoring of continuous temperature recording, regular verification of proper functioning of the alarms, renewal of the characterizations of the refrigerated cabinet), calibrating the thermometers, and putting in place preventive maintenance procedures. The second critical failure mode was a power outage, for which the main action proposed was installation of an audible alarm system. A remedial procedure in case of a break in the cold chain and the establishment of a preventive maintenance schedule for electrical installations were also proposed. Saint-Lorant and others[11] planned to group temperature-sensitive drugs into categories according to their stability, to allow their retrieval in case of a break in the cold chain. The third critical failure mode was the storage of boxes containing temperature-sensitive drugs in the refrigerated cabinet, a situation in which the temperature could exceed 8°C. To address this potential failure mode, staff were asked to unpack the drugs quickly before storing them.

The stage of storage in the various pharmacy units had 3 critical failure modes according to the Pareto law: a difference between the temperature displayed by the thermometer and the actual temperature, power outage, and refrigerator door not closed properly. The proposed improvement actions were to train staff and ensure preventive maintenance of equipment.

Storage in the patient care units represents the penultimate stage of the medication-use process; it is crucial because it is the last step before drug administration. This stage also had the greatest number of failure modes of any stage: there were 9 failures, 5 of which were critical according to the Pareto law: difference between the temperature displayed by the thermometer and actual temperature, required temperature not reached in refrigerator, medication left outside the refrigerator before storage, inadequate storage in the refrigerator (e.g., in the door or the vegetable drawer), and refrigerator door not closed properly. The corrective actions were as follows: training of paramedical staff and sensitization to the challenges of the cold chain, monitoring the temperature of refrigerators 3 times daily, and returning to the pharmacy any temperature-sensitive drugs not administered to patients (to avoid cluttering refrigerators on the care units). Regular pharmaceutical audits within the various clinical services have also been proposed. Saint-Lorant and others[11] have also provided for pharmaceutical audits in clinical services to remedy fault points and to put in place any corrective actions needed to improve the cold chain.

Similar to other work using FMECA,[26,27] subjectivity in the rating of each risk was the main limitation of this study. In fact, the identification of failure modes and their rating are mainly based on the risk perceptions of various health care professionals, given that everyone participates and reacts according to their own experience.

CONCLUSION

In this study, storage in patient care units was the stage of the medication-use process with the most critical failure modes and required the most interventions to ensure patient safety. Securing this high-risk process is a means of ensuring the efficiency of patient care within the framework of continuous quality improvement. Admittedly, implementation of quality improvement measures appears to be difficult, time-consuming, and expensive; however, such an approach makes it possible to prevent the deterioration of temperature-sensitive drugs and thus to reduce the financial losses due to breakdown of the cold chain. A second FMECA should be carried out to reassess the medication-use process after implementation of improvement actions.

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Impact of Pharmacist-Directed Medication Reconciliation in Reducing Medication Discrepancies: A Randomized Controlled Trial

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ABSTRACT

Background: In hospital surgical wards, patients are at higher risk for medication errors, in part because physicians may not consider themselves sufficiently trained to prescribe medications. Hence, collaborative teamwork involving the pharmacist is needed.

Objectives: To assess the impact of medication reconciliation directed by pharmacists on decreasing medication discrepancies after discharge from the surgical ward.

Methods: Patients admitted to the surgical unit at a tertiary teaching hospital in Amman, Jordan, between July 2017 and July 2018 were selected and randomly assigned to either the control or the intervention group. Upon admission, the number and kinds of unintentional medication discrepancies were determined for both groups. Medication reconciliation was then provided to patients in the intervention group. The number of unintentional discrepancies was re-evaluated upon discharge for both groups. To assess differences between the control and intervention groups, the χ^2 or Fisher exact test was used for categorical variables and an independent-sample *t* test for continuous data. A paired *t* test was conducted to determine whether the number of medication discrepancies was reduced as a result of pharmacists' recommendations.

Results: A total of 123 patients met the inclusion criteria, 61 in the intervention group and 62 in the control group. Discrepancies of omission and wrong dose constituted 41 (77%) of the 53 discrepancies in the intervention group and 25 (76%) of the 33 discrepancies in the control group. The number of unintentional discrepancies was significantly reduced from admission to discharge in both the intervention group ($p = 0.002$) and the control group ($p = 0.007$). Of 53 recommendations made by pharmacists, 20 (38%) were accepted by the treating physician, and all of these discrepancies were resolved.

Conclusions: This study sheds light on the existence of unintentional medication discrepancies upon admission for surgical patients, which may expose the patients to potential harm upon discharge from hospital. Additional studies with a larger sample size are needed to gain further insights on pharmacists' role in implementing medication reconciliation for surgical patients.

Keywords: medication reconciliation, discrepancies, surgery, pharmacists

Trial Registration: ClinicalTrials.gov NCT03928106

RÉSUMÉ

Contexte : Dans les services chirurgicaux des hôpitaux, les patients sont exposés à un risque d'erreurs de médication plus élevé, en partie parce que les médecins ne se considèrent pas suffisamment formés pour prescrire des médicaments. Par conséquent, un travail d'équipe collaboratif impliquant le pharmacien est nécessaire.

Objectifs : Évaluer l'impact du bilan comparatif des médicaments dirigé par les pharmaciens sur la diminution des écarts médicamenteux après la sortie du service de chirurgie.

Méthodes : Les patients admis à l'unité chirurgicale d'un hôpital d'enseignement tertiaire à Amman, en Jordanie, entre juillet 2017 et juillet 2018 ont été sélectionnés et affectés au hasard au groupe témoin ou au groupe d'intervention. Lors de l'admission, le nombre et les types de divergences médicamenteuses non intentionnelles ont été définis pour les deux groupes. Le bilan comparatif des médicaments a ensuite été fourni aux patients du groupe d'intervention. Le nombre d'écarts non intentionnels a été réévalué à la sortie pour les deux groupes. Pour évaluer les différences entre le groupe témoin et le groupe d'intervention, le test χ^2 ou le test exact de Fisher a été utilisé pour les variables catégorielles et un test *t* pour échantillon indépendant, pour les données continues. Un test *t* apparié a été effectué pour déterminer si le nombre d'écarts de médicaments a été réduit à la suite des recommandations des pharmaciens.

Résultats : Au total, 123 patients répondaient aux critères d'inclusion : 61 dans le groupe d'intervention et 62 dans le groupe témoin. Les divergences d'omission et de mauvaise dose constituaient 41 (77 %) des 53 divergences dans le groupe d'intervention et 25 (76 %) des 33 divergences dans le groupe témoin. Le nombre d'écarts non intentionnels a été significativement réduit de l'admission à la sortie à la fois dans le groupe d'intervention ($p = 0{,}002$) et dans le groupe témoin ($p = 0{,}007$). Sur 53 recommandations émises par des pharmaciens, 20 (38 %) ont été acceptées par le médecin traitant et toutes ces divergences ont été résolues.

Conclusions : Cette étude met en lumière l'existence d'écarts médicamenteux non intentionnels lors de l'admission des patients chirurgicaux, ce qui peut exposer les patients à des risques au moment de leur sortie de l'hôpital. D'autres études avec un échantillon plus important sont nécessaires pour mieux comprendre le rôle des pharmaciens dans la mise en œuvre du bilan comparatif des médicaments pour les patients chirurgicaux.

Mots-clés : bilan comparatif des médicaments, divergences, chirurgie, pharmaciens

Enregistrement de l'essai : ClinicalTrials.gov NCT03928106

INTRODUCTION

Medication reconciliation is a practice whereby health care workers cooperate with patients, their family members, and other health care workers to ensure that precise, complete drug information is transferred consistently through transitions of care.[1] It requires an extensive review of preadmission medications for each patient and comparison with current (in-hospital) medications to ensure that any added, changed, or discontinued medications are carefully checked.[2-4] Hence, medication reconciliation is an established practice to verify the use of medications, to identify and resolve harmful unintended discrepancies, and thus to decrease medication errors during transitions in patient care.[3,5,6]

Medication reconciliation must be performed at each transition of care, especially when new medications are ordered or existing orders are renewed.[2] An accurate medication list (with drug names, dosages, frequencies, and routes of administration) is prepared at the time of hospital admission to evaluate and manage avoidable medication errors, such as duplication of therapy, dosage errors, omission (without clinical justification) of drugs for which the patient has preadmission indications, errors of commission, and drug–drug interactions during the hospital stay (on admission and transfer) and after patient discharge.[2,6-8] Identified discrepancies can be classified as intentional (documentation errors) or unintentional.[9]

Pharmacists have become more active in providing patient care services, including medication reconciliation.[9] These health care providers represent a cornerstone in the provision of essential information about the safe and effective use of medications, and their engagement in patient care during hospital rounds has been essential in improving medication safety.[10] Because pharmacists are specialists in drug use, their involvement in obtaining patient drug histories has led to lower rates of medication discrepancies and has improved the effectiveness of identifying and resolving these discrepancies, relative to histories obtained by other health care providers.[6] Inaccurate reconciliation and medication history-taking can lead to medication errors.[8] As one of the main causes of morbidity in inpatient settings, medication errors must be prevented through all available means, starting with pharmacist involvement.[3,9]

Compared with internal medicine wards, the surgical wards in hospitals present greater risks of medication errors for patients.[11] Only a few studies have investigated medication discrepancies among surgical patients, and these have revealed high discrepancy rates.[12,13] For example, a study conducted in surgical intensive care units found a total of 325 discrepancies for 45 patients (average of 7.2 discrepancies per patient).[12] Another study, involving patients who had undergone gastrointestinal surgery, found an average of 3.4 discrepancies per patient. [13] Patients in the surgical ward have greater need for medications to control pain, such as opioids, as well as for antibiotics, antithrombotic drugs, and cardiovascular drugs.[14,15] The care of these patients is usually delivered by junior physicians, who are not yet adequately trained in the prescription of medications and are usually supervised by specialists who may have inadequate experience in complex pharmacotherapy.[16,17] Hence, collaborative teamwork involving clinical pharmacists in the surgical wards is needed.[18,19]

Pharmacists have an important role in reviewing preoperative medications, before their administration, to ensure appropriate selection, recognition of drug–drug interactions and drug allergies, and weight-based hepatic or renal dosage adjustments to reduce complications related to surgical procedures.[20] Only one previous study has investigated the impact of pharmacist-led medication reconciliation on reducing discrepancies for surgical patients; the study found no significant change in medication errors before and after the intervention.[21] Thus, further studies are needed to examine the effectiveness of implementing pharmacist-led medication reconciliation among surgical patients.

The aim of the current study was to evaluate the frequency and types of medication discrepancies identified by clinical pharmacists in the surgical ward of a teaching hospital in Amman, Jordan, and to determine the effect of a medication reconciliation service delivered by clinical pharmacists in reducing the medication discrepancies that were identified.

METHODS

Study Design, Participants, and Clinical Setting

This single-blind randomized controlled trial took place at Jordan University Hospital (JUH) over the period July 2017 to July 2018. JUH is a 600-bed tertiary teaching hospital located in Amman, Jordan.

Two hundred patients admitted to the surgical department were approached and screened for inclusion. Patients were included in the study if they were at least 18 years old, were using at least 4 long-term medications regularly before admission, spoke Arabic, were expected to stay in hospital for at least 48 hours, and did not have any cognitive impairment. Patients who were in isolation, those who discharged themselves against medical advice, and those who refused to provide written informed consent were excluded.

The study was registered with clinicalTrials.gov (registration identifier NCT03928106), and ethics approval was obtained from the Institutional Review Board at the JUH (reference number 65/2017).

Sample Size Calculation

The sample size was estimated according to outcomes of a previous study by the same research team, which assessed the impact of medication reconciliation performed by pharmacists on the number of medication discrepancies

for internal medicine patients.[22] In that study, the pooled standard deviation (SD) for the number of unintentional discrepancies for the intervention and control groups was 0.92. To determine the necessary sample size, with α set at 0.05 and power of 80% (the most commonly used values for these parameters),[23] the following equation was used:

$$N = 2\,\sigma^2\,(Z_{\text{Critical}} + Z_{\text{Power}})^2/D^2$$

where N is the sample size, σ is the pooled SD for the 2 groups, ZC_{ritical} is 1.96 for the 0.05 significance level, Z_{Power} is 0.842 for 80% statistical power, and D is the minimum expected difference between the 2 means (set at 0.5).

According to this equation, the minimum required sample size to obtain a significant difference was calculated as 53 participants per group. We assumed a potential 20% attrition rate, and aimed to recruit 11 more participants for each group to compensate for any possible attrition. Therefore, a sample of 64 patients was to be recruited for each group.

Randomization, Data Collection, and Identification of Medication Discrepancies

Patients who met the inclusion criteria were informed about the purpose of the research, were told that participation was voluntary and that responses would be kept anonymous, and were asked to provide written informed consent.

Data were collected by 2 clinical pharmacist preceptors at JUH (R.Y., Z.S.). These pharmacists were well trained in data collection and in identifying and resolving medication discrepancies in a standardized, systematic manner. The training included a didactic lecture, followed by a simulation training session.

All of the patients were recruited in the JUH surgical ward after undergoing their scheduled surgeries. Following recruitment, the patients were randomly assigned to the intervention or the control group, according to a random number table generated by the Statistical Package for the Social Sciences (SPSS), version 22 (IBM SPSS Statistics). A specific data collection form was used to gather patient-specific information, including sociodemographic data (age, sex, marital status, educational level, monthly income, smoking status, and nationality), medical data (admission date, intended length of stay, acute and chronic medical conditions, current admission medications, preadmission medication history [i.e., best possible medication history or BPMH], and discharge date). Various sources were used to obtain the BPMH, including patient and caregiver interviews, medical records, and physician interviews. Patients' 10-year mortality rate was predicted from the Charlson comorbidity index,[24] as calculated by the researchers. A flowchart for data collection is presented in Figure 1.

Medication discrepancies were identified for each patient in both groups by comparing the patient's current (in-hospital) medication order with their BPMH. The discrepancies were categorized as intentional undocumented or unintentional. Unintentional discrepancies were reported as "medication errors", and intentional discrepancies were recorded as "documentation errors". To ensure consistency in identifying medication discrepancies, some cases from each of the clinical pharmacists were re-evaluated independently by another researcher (R.A.); no differences were found.

Unintentional discrepancies were further categorized into different types, including addition, duplication, omission, wrong drug, wrong dose, and wrong frequency. They were also classified according to the seriousness levels defined by Cornish and others[25]: "Class 1 discrepancies were those unlikely to cause patient discomfort or clinical deterioration. Class 2 discrepancies were those with the potential to cause moderate discomfort or clinical deterioration, and class 3 discrepancies were those with the potential to cause severe discomfort or clinical deterioration."

Pharmacist-Delivered Intervention

For patients in the intervention group, pharmacists discussed the discrepancies identified and provided their recommendations to the responsible clinicians using a consult form. If the clinicians accepted the recommendation, it was documented as an "accepted recommendation". Finally, upon discharge the number of medication discrepancies was assessed for each patient in both groups.

Statistical Analysis

SPSS software, version 22, was used to analyze the data. Normality was checked with the Shapiro–Wilk test. Descriptive analysis was based on means and SDs for continuous variables and percentages for categorical variables.

The χ^2 or Fisher exact test was used to assess differences between the control and intervention groups for categorical variables, and an independent-sample t test was used for continuous data. A paired t test was conducted to determine whether the number of medication discrepancies was reduced as a result of the pharmacists' recommendations. A p value of less than 0.05 was considered statistically significant with 2-tailed tests.

RESULTS

During the study period, a total of 200 patients were screened, of whom 123 matched the study inclusion criteria; all of these patients agreed to participate (100% participation rate). Of the 123 participants, 61 (49.6%) were assigned to the intervention group, and the remaining 62 (50.4%) were assigned to the control group.

The average age of the study population was 61.9 years (SD 10.0). Men represented slightly more than half of the patients (n = 63, 51.2%). Most of the participants were married (n = 104, 84.6%), most did not smoke (n = 95, 77.2%), and the level of education was a postsecondary diploma or higher for 20.3% (n = 25) (Table 1).

Medical characteristics and administrative data are displayed in Table 2, which shows that the 2 groups did not differ significantly with regard to intended length of stay in hospital, number of medical conditions, number of current or home medications, number of documentation errors, actual length of hospital stay, Charlson comorbidity index, or number of prescribed medications upon discharge ($p \geq 0.05$ for all).

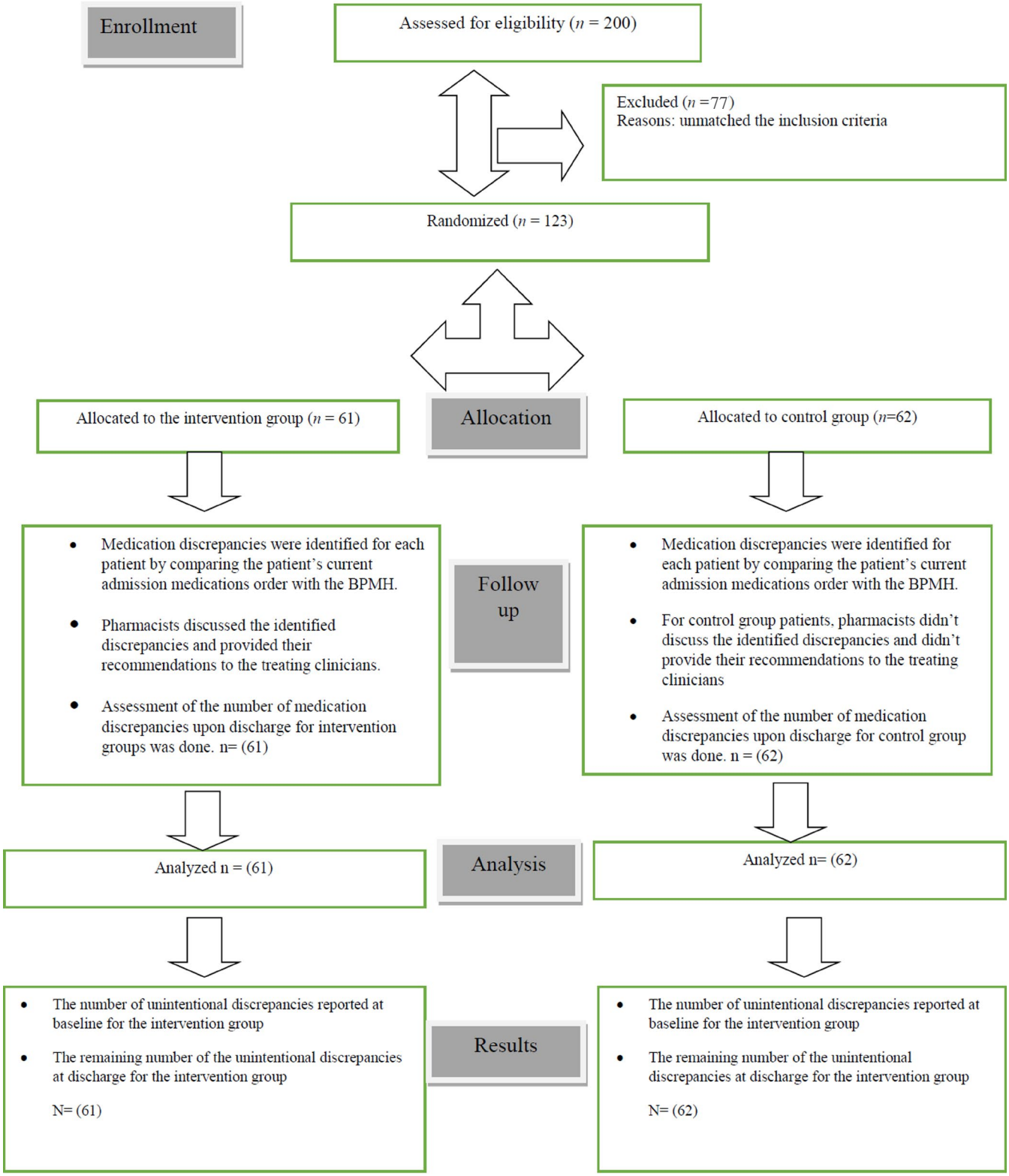

FIGURE 1. Flowchart for data collection. Patients were assessed for eligibility and recruited for study participation after undergoing scheduled surgery. BPMH = best possible medication history.

Table 3 classifies the type and prevalence of unintentional discrepancies (medication errors) detected for both groups, along with their clinical seriousness. The total number of discrepancies was 86, of which 53 (62%) occurred in the intervention group and 33 (38%) in the control group.

With regard to the types of medication discrepancies detected in the intervention group, the most common was omission ($n = 32$, 60%) followed by wrong dose ($n = 9$, 17%). The same pattern was observed for the control group, for which omissions represented the more than half of the discrepancies ($n = 18$, 55%), followed by wrong dose ($n = 7$, 21%). Overall, discrepancies of omission and wrong dose constituted 41 (77%) of the 53 discrepancies in the intervention group and 25 (76%) of the 33 discrepancies in the control group. Among the 53 medication discrepancies in the intervention group, moderate to severe harmful discrepancies (classes 2 and 3) accounted for 30 (57%). Among the 33 medication discrepancies in the control group, 16 (48%) were classified as moderate to severe harmful discrepancies. This difference was not statistically or clinically significant ($p = 0.35$).

Table 4 shows the number of unintentional discrepancies reported at baseline (i.e., at time of admission) and the number of unintentional discrepancies remaining at discharge for the intervention and control groups. In terms of unintentional discrepancies recorded at baseline, the average number was greater in the interventional group (0.86, SD 1.40) than in the control group (0.53, SD 0.65). This observed difference in the average number of unintentional discrepancies was not statistically significant ($p = 0.09$).

The average number of unintentional discrepancies remaining at discharge was 0.68 (SD 1.35) in the intervention

TABLE 1. Demographic Characteristics of Study Sample at Baseline

Characteristic	Group; No. (%) of Patients[a] Intervention ($n = 61$)	Control ($n = 62$)	Total ($n = 123$)	p Value[b]
Age (mean ± SD	62.1 ± 8.6	61.8 ± 11.3	61.9 ± 10.0	0.87[c]
Sex				
Women	29 (47.5)	31 (50.0)	60 (48.8)	0.78
Men	32 (52.5)	31 (50.0)	63 (51.2)	
Marital status				0.022
Single	2 (3.3)	6 (9.7)	8 (6.5)	
Married	53 (86.9)	51 (82.3)	104 (84.6)	
Divorced	0 (0)	4 (6.5)	4 (3.3)	
Widowed	6 (9.8)	1 (1.6)	7 (5.7)	
Education				0.232
None	6 (9.8)	5 (8.1)	11 (8.9)	
Primary/high school	38 (62.3)	44 (71.0)	82 (66.7)	
Diploma/bachelor's degree	15 (24.6)	8 (12.9)	23 (18.7)	
PhD	2 (3.3)	0 (0.0)	2 (1.6)	
Missing data	0 (0.0)	5 (8.1)	5 (4.1)	
Monthly income (JOD)				0.67
1–250	56 (91.8)	55 (88.7)	111 (91.2)	
251–500	3 (4.9)	5 (8.1)	8 (6.5)	
501–750	0 (0.0)	0 (0.0)	0 (0.0)	
751–1000	1 (1.6)	2 (3.2)	3 (2.4)	
Missing data	1 (1.6)	0 (0.0)	1 (0.8)	
Smoking				0.21
Yes	11 (18.0)	17 (27.4)	28 (22.8)	
No	50 (82.0)	45 (72.6)	95 (77.2)	
Nationality				0.30
Jordanian	58 (95.1)	61 (98.4)	119 (96.7)	
Other	3 (4.9)	1 (1.6)	4 (3.3)	

JOD = Jordanian dinars, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Pearson χ^2 test, except where indicated otherwise.
[c]Independent-sample t test.

group compared with 0.41 (SD 0.62) in the control group. This difference was also statistically nonsignificant ($p = 0.16$).

When the number of unintentional discrepancies at baseline was compared with the number of unintentional discrepancies remaining at discharge, the results revealed statistically significant reductions for both groups ($p = 0.002$ for the intervention group; $p = 0.007$ for the control group). However, the extent of the reduction was not significantly different between the intervention and control groups ($p = 0.33$) (Table 4).

TABLE 2. Medical History and Administrative Data at Baseline

	Group; Mean ± SD			
Variable	**Intervention (*n* = 61)**	**Control (*n* = 62)**	**Total (*n* = 123)**	***p* Value[a]**
Intended length of stay (days)	5.0 ± 5.4	4.1 ± 2.1	4.5 ± 4.1	0.26
No. of medical conditions	3.6 ± 1.4	3.3 ± 1.5	3.4 ± 1.4	0.24
No. of current medications	8.6 ± 3.1	7.9 ± 2.8	8.2 ± 3.0	0.15
No. of home medications	7.2 ± 3.0	6.6 ± 2.3	6.9 ± 2.7	0.22
No. of documentation errors	2.5 ± 1.7	2.0 ± 1.7	2.3 ± 1.7	0.15
Length of stay (days)	9.6 ± 11.0	6.7 ± 5.4	8.1 ± 8.7	0.07
Charlson comorbidity index score	3.5 ± 1.7	3.2 ± 1.7	3.3 ± 1.7	0.41
No. of discharge medications	7.1 ± 3.0	6.7 ± 2.5	6.9 ± 2.8	0.40

SD = standard deviation.
[a]Independent-sample *t* test.

TABLE 3. Types and Clinical Seriousness of Unintentional Medication Discrepancies at Baseline

	Group; No. (%) of Patients		
Variable	**Intervention (*n* = 53)**	**Control (*n* = 33)**	***p* Value[a]**
Type of discrepancy			0.14
Wrong drug	3 (6)	0 (0)	
Wrong dose	9 (17)	7 (21)	
Wrong frequency	1 (2)	5 (15)	
Omission	32 (60)	18 (55)	
Addition	7 (13)	3 (9)	
Duplication	1 (2)	0 (0)	
Seriousness of error			0.35
Class 1	23 (43)	17 (52)	
Class 2	28 (53)	16 (48)	
Class 3	2 (4)	0 (0)	

[a]Fisher exact test.

TABLE 4. Unintentional Discrepancies at Baseline and at Discharge

	No. of Unintentional Discrepancies (Mean ± SD)			
Variable	**Baseline**	**Discharge**	**Reduction**	***p* Value[a]**
Intervention group (*n* = 61)	0.86 ± 1.40	0.68 ± 1.35	0.18 ± 0.43	0.002
Control group (*n* = 62)	0.53 ± 0.65	0.41 ± 0.62	0.11 ± 0.32	0.007
p value comparing the 2 groups[b]	0.09	0.16	0.33	–

SD = standard deviation.
[a]Paired sample *t* test.
[b]Independent-sample *t* test.

Among the submitted recommendations, 20 out of 53 (38%) were accepted by the treating physician, and all of them led to resolution of the medication discrepancy. It should be noted that in this study, the clinical pharmacists were instructed to not intervene to resolve unintentional discrepancies in the control group, unless the discrepancies were classified as severe (class 3). No class 3 discrepancies were identified in the control group, so the clinical pharmacists performed no interventions for patients in this group.

DISCUSSION

To the authors' knowledge, this study was the first randomized controlled trial in Jordan to assess the impact of providing medication reconciliation services to patients in surgical wards.

During the study period, a total of 86 discrepancies were identified in the 2 groups combined, with an overall average of 0.7 discrepancies per patient. The overall average of medication discrepancies has varied across previous studies.[7,9,26,27] A recent study conducted at JUH reported a similar average of 0.72 unintentional discrepancies per patient.[9] Other studies have reported higher rates of unintentional discrepancies, from 1.5 to 2.3 per patient.[7,26,27] This variation could be due to differences in the evaluation and identification of medication discrepancies among the researchers. Another factor may be that JUH is accredited by the Joint Commission International, which requires fulfilment of various standards that may reduce the incidence of medication discrepancies.

The results of the present study revealed that unintentional discrepancies were reduced from admission to discharge in both the intervention group (p = 0.002) and the control group (p = 0.007). This might be because the implementation of medication reconciliation services has increased awareness about detecting medication errors, which will be reflected across the entire patient population. Other studies have revealed significant improvements in patient safety as a result of the involvement of pharmacists as active health care providers, specifically in terms of reducing medication discrepancies.[5,6,28]

Discrepancies involving omissions and wrong doses represented the majority of unintentional discrepancies detected in both groups. This is a worrisome finding and is comparable to the results of previous studies, in which researchers reported that drug omissions were the most important type of error detected, followed by wrong doses.[29,30]

The seriousness of the recognized discrepancies was also assessed. About half of the reported unintentional discrepancies in both groups were deemed moderate to severe (57% in the intervention group, 48% in the control group), as they had the potential to cause harm or worsening of the patient's condition. Similar findings have been reported from Canada and Saudi Arabia, with most of the reported discrepancies being classified as serious.[31,32] However, other studies in Ireland and France categorized the majority of the discrepancies as having minor to moderate seriousness.[33,34] The potentially serious nature of the majority of discrepancies means that medication reconciliation services should start from the time of admission to prevent patient harm.

For the intervention group, discussion with the responsible physician was based on written forms documenting the reported unintentional discrepancies. Of the 53 interventions recommended to physicians, 20 (38%) were accepted and the discrepancy was resolved. This result was lower than those of previous research (93%[3] and 72%[35]). Nonetheless, despite the modest acceptance of pharmacists' recommendations in the present study, the number of unintentional discrepancies for the intervention group was significantly reduced upon discharge relative to the number of unintentional discrepancies at baseline.

The outcomes of this study will be added to existing research in this field, assessing the importance of the pharmacist in identifying medication discrepancies and in avoiding medication errors in the hospital setting.[9,36,37] In Jordan and neighbouring countries, previous studies have shown readiness among health care teams to interact with pharmacists to provide a medication reconciliation service.[38]

Limitations

This study had several limitations. It was conducted in a single teaching hospital, which might affect the generalizability of the results. Other studies in different hospitals throughout the country are needed. The detection of unintentional discrepancies and classification of their severity was completed by only 2 pharmacists and relied on the researchers' subjective judgment, which may raise concerns about bias. There was also a possibility of the Hawthorne effect, whereby clinicians' knowledge that their work was being observed might have caused a reduction in the number of unintentional medication discrepancies in both groups. This could be considered as a limitation of the validity of some of the assessed outcomes. Finally, the clinical pharmacists were not blinded to the randomization table, which leads to the possibility of selection bias.

CONCLUSION

This study sheds light on the presence of unintentional medication discrepancies among surgical patients upon their admission to hospital, which might expose them to harm upon discharge. Moreover, the study highlighted a significant reduction, from admission to discharge, in the number of medication discrepancies for both the intervention and control groups. It also showed that clinical pharmacists had a positive impact in resolving unintentional discrepancies. Further studies with larger sample sizes are needed to gain

better insight into the pharmacist's role in implementing medication reconciliation for surgical patients.

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Risk Factors, Screening, Diagnosis, and Treatment of Osteoporosis in HIV-Infected Adults in an HIV Primary Care Clinic

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ABSTRACT

Background: The population of people living with HIV is aging, and with aging come emergent comorbidities, including osteoporosis, for which screening and treatment are becoming increasingly important. Osteoporosis prevalence among those living with HIV is 3 times greater than among HIV-uninfected controls.

Objective: To assess and describe osteoporosis risk factors, screening, diagnosis, and treatment for people 50 years of age or older living with HIV and receiving care at a multidisciplinary HIV primary care clinic.

Methods: A retrospective chart review of people 50 years of age or older living with HIV was conducted at the John Ruedy Clinic in Vancouver, British Columbia, between June 1, 2016, and June 1, 2019. Patients who had had fewer than 2 yearly follow-up appointments were excluded.

Results: A total of 146 patients were included in the analysis; most were male (n = 134, 92%), and the median age was 55 years. Patients had a median of 3 osteoporosis risk factors (in addition to age and HIV infection), and 145 patients had at least 1 risk factor. All screening for osteoporosis was conducted by dual-energy X-ray absorptiometry (DXA). Thirty-nine (27%) of the patients were screened with DXA, 92 (63%) were not screened, and 15 (10%) already had a diagnosis of osteoporosis. The DXA screening identified osteoporosis in an additional 10 patients and osteopenia in 22 patients. Treatments for patients with osteoporosis included bisphosphonates (n = 15, 60%) and vitamin D or calcium (or both), without any other medications (n = 4, 16%). In the overall study population, 32 (22%) of the patients were taking calcium and 46 (32%) were taking vitamin D.

Conclusions: Many patients aged 50 years or older and receiving HIV care at the John Ruedy Clinic had or were at risk for osteoporosis. An opportunity exists to increase screening and treatment of these individuals. A multidisciplinary team may be crucial in achieving this goal.

Keywords: HIV, osteoporosis, risk factors, screening, treatment

RÉSUMÉ

Contexte : La population des personnes vivant avec le VIH vieillit et, avec le vieillissement, des comorbidités émergent, dont l'ostéoporose, pour laquelle le dépistage et le traitement sont de plus en plus importants. La prévalence de l'ostéoporose chez les personnes vivant avec le VIH est 3 fois plus élevée que chez les témoins non infectés.

Objectif : Évaluer et décrire les facteurs de risque, le dépistage, le diagnostic et le traitement de l'ostéoporose chez les personnes d'au moins 50 ans vivant avec le VIH et qui reçoivent des soins dans une clinique pluridisciplinaire de soins primaires pour le VIH.

Méthodes : Un examen rétrospectif des dossiers des personnes d'au moins 50 ans vivant avec le VIH a été effectué à la clinique John Ruedy à Vancouver (Colombie-Britannique) entre le 1er juin 2016 et le 1er juin 2019. Les patients qui avaient eu moins de 2 rendez-vous de suivi annuels ont été exclus de l'étude.

Résultats : Au total, 146 patients ont été inclus dans l'analyse; la plupart étaient des hommes (n = 134, 92 %) et l'âge médian était de 55 ans. Les patients avaient une médiane de 3 facteurs de risque d'ostéoporose (en plus de l'âge et de l'infection par le VIH), et 145 patients avaient au moins 1 facteur de risque. Tous les dépistages de l'ostéoporose ont été réalisés par absorption biphotonique à rayons X (DXA). Trente-neuf patients (27 %) ont été dépistés par DXA, 92 (63 %) ne l'ont pas été et 15 (10 %) avaient déjà un diagnostic d'ostéoporose. Le dépistage par DXA a permis d'identifier l'ostéoporose chez 10 patients supplémentaires et l'ostéopénie chez 22 patients. Le traitement des patients atteints d'ostéoporose comprenait des bisphosphonates (n = 15, 60 %) et de la vitamine D ou du calcium (ou les deux) sans autre médicament (n = 4, 16 %). Dans la population générale de l'étude, 32 patients (22 %) prenaient du calcium et 46 (32 %) prenaient de la vitamine D.

Conclusions : De nombreux patients d'au moins 50 ans recevant des soins pour le VIH à la clinique John Ruedy présentaient un risque d'ostéoporose ou l'avaient déjà développée. Il est possible d'accroître leur dépistage et leur traitement, et une équipe multidisciplinaire peut être cruciale pour atteindre cet objectif.

Mots-clés : VIH, ostéoporose, facteurs de risque, dépistage, traitement

INTRODUCTION

The population of people living with HIV is aging, and the management of comorbidities is becoming an increasingly important part of their care. One significant consideration is bone mineral density (BMD) and osteoporosis. In the general population, osteoporosis accounts for 80% of fragility fractures in menopausal women over age 50 years. Among men over the age of 60 years, there is a 25% chance of osteoporotic fracture, and such fractures can lead to significant mortality, morbidity, and health care costs.[1] People living with HIV have a higher risk of low BMD and fragility fractures than those without HIV infection. HIV is included as a risk factor for osteoporosis in the guidelines of the US National Osteoporosis Foundation (now known as the Bone Health and Osteoporosis Foundation).[2] A meta-analysis of pooled prevalence data from the HIV population showed decreased BMD in 67% of patients and osteoporosis prevalence of 15% (3 times greater than that of HIV-uninfected controls).[3]

Lower BMD among people living with HIV can be explained by the prevalence of conventional risk factors, pathophysiological changes in HIV, and treatment with antiretroviral therapy (ART). Traditional risk factors for osteoporosis, such as low body weight and cigarette smoking, are more common among people living with HIV.[4] In addition, the pro-inflammatory state of HIV affects bone formation and resorption.[5] ART is associated with a 2% to 6% decrease in BMD during the first 2 years of treatment.[6] Tenofovir disoproxil fumarate (TDF) and boosted protease inhibitors have been associated with decreased BMD, with TDF having the strongest association.[7] Tenofovir alafenamide is a prodrug of tenofovir associated with significantly lower decrease in BMD than occurs with TDF[8,9]; it may be an attractive alternative for those withosteoporosis.[10]

Many factors can affect bone health, and a thorough assessment is warranted to screen for risk factors and to detect early decreases in BMD. Within the general population, individuals at high risk of osteoporotic fractures can be screened with a fracture risk assessment tool (FRAX) or dual-energy x-ray absorptiometry (DXA). Osteoporosis can be diagnosed on the basis of a history of fragility fracture or by measuring BMD with DXA. According to McComsey and others,[7] the World Health Organization (WHO) classifies BMD as normal, osteopenia, or osteoporosis according to the number of standard deviations below the mean BMD for a healthy, young, sex- and ethnicity-matched reference population. Canadian guidelines recommend DXA for adults under age 50 if they have particular risk factors, including fragility fracture, prolonged use of glucocorticoids, or use of other high-risk medications.[11] For adults over age 50, screening with DXA is indicated if any of the aforementioned risk factors are present, or the risk factors of smoking, high alcohol intake, or low body weight. All adults over age 65 should undergo BMD testing.[11]

The recommendations in published guidelines for osteoporosis screening in people living with HIV are comparable to those for the general population. The primary care guidelines of the BC Centre for Excellence in HIV/AIDS[10] suggest screening for individuals 50 years of age or older, which is consistent with the Canadian osteoporosis guidelines.[11] This differs from the approach offered by Brown and others,[4] who recommended screening with FRAX for people living with HIV who are 40 to 49 years old. Unfortunately, there is no validated screening tool for use in patients living with HIV, and FRAX is known to underestimate the risk of fracture for this population.[12-14] Brown and others[4] recommended DXA for those with a FRAX score above 10%, as well as those with additional risk factors (men ≥ 50 years old, postmenopausal women, and those with a history of fragility fracture, long-term steroid use, or high risk of falls). Diagnosis of osteoporosis in people living with HIV follows the same criteria as those outlined by the WHO.

Treatment of osteoporosis in people living with HIV is the same as outlined in national guidelines for persons not infected with HIV. The foundation of bone health relies on adequate intake of calcium (1200 mg daily) and vitamin D (800–2000 IU daily), as well as lifestyle measures, including weight-bearing exercises and smoking cessation, both of which should be assessed for all patients. For patients with a history of fragility fracture or high fracture risk as indicated by FRAX score (> 20% risk of fracture in 10 years) or DXA (T-score ≤ –2.5), antiresorptive therapy should be considered.[3,11,15] Bisphosphonates are considered first-line therapy because of their long-term efficacy and good safety profile. Denosumab is commonly used to treat osteoporosis in the general population, but there are few efficacy data, and this drug is associated with potential for increased risk of infection; as such, its use by people living with HIV has been limited.[4,16] For patients with low BMD, a history of fragility fracture, or osteoporosis, an ART regimen that avoids TDF and protease inhibitors should be considered.[13]

The John Ruedy Clinic at St Paul's Hospital in Vancouver, British Columbia, is a low-barrier multidisciplinary HIV primary care clinic. It hosts approximately 1300 active patients and includes primary care physicians, pharmacists, nurses, dieticians, and access to specialists such as endocrinologists, psychiatrists, and nephrologists. Although many of these patients have immediate urgent needs, screening and treatment for chronic diseases such as osteoporosis is becoming a significant part of their care, given the aging of the population. The purpose of this study was to assess risk factors for osteoporosis, as well as pertinent screening, diagnosis, and treatment, among HIV clinic patients at least 50 years of age.

METHODS

This single-centre retrospective chart review was conducted at the John Ruedy Clinic in Vancouver. Electronic medical

records were used to identify eligible patients. Participants were considered eligible if they were HIV-positive, 50 years of age or older as of June 1, 2016, and an active patient at the clinic during the study period of June 1, 2016, to June 1, 2019. Patients were excluded if they had had fewer than 2 yearly follow-up appointments with a clinic physician, as this low frequency would provide insufficient opportunity for thorough assessment. This study was approved by the local research ethics board, with a waiver of informed consent.

The planned sample size was 170 patients (147 patients plus 15% to account for attrition), calculated from the population of 582 clinic patients who were 50 years of age or older. The confidence interval was 95% with a margin of error of 7%. A random sample of clinic patients was drawn using Excel spreadsheet software (Microsoft Corporation).

All data were collected from the clinic's electronic medical records by a single reviewer (K.K.), and data collection for 15% of the charts was audited by a second reviewer (C.O.). The collected data included patient history, medications, medical conditions, results of medical testing, specialist consults, and chart notes prepared by the multidisciplinary team. Data were also collected for osteoporosis risk factors, screening, diagnosis, treatment recommendations, and care team members involved. The risk factors were adapted, before the chart review began, from "A Tool for Preventing and Managing Bone Disease in HIV-Infected Adults"[13] (factors are listed in Table 1). Any of the following qualified as screening: annual measurement of height and weight, FRAX scores, DXA scans, fall risk assessments, and laboratory assessments for differential diagnosis (e.g. thyroid-stimulating hormone, complete blood count). CAROC scores (Osteoporosis Canada's 10-year fracture risk scores) were recorded if they appeared in the DXA scan report. The investigators calculated FRAX scores for all patients using the University of Sheffield calculator, with HIV included as a secondary cause.[17]

The primary outcomes of this study were the numbers of patients screened for osteoporosis, given a diagnosis of osteoporosis, treated for osteoporosis with bisphosphonates, and given a recommendation for supplementation with calcium and vitamin D. The secondary outcomes were the number of patients with osteoporosis risk factors in addition to HIV and age, the specific types of risk factors, the types of screening done, the number of recommendations provided for bone health other than bisphosphonates and calcium/vitamin D, and the team members involved in the assessment of bone health.

Data were collected using Access database software (Microsoft Corporation) and analyzed using descriptive statistics in Excel spreadsheet software.

RESULTS

Of 170 charts screened, 146 charts met the inclusion criteria. Of those excluded, 21 patients joined the clinic after

TABLE 1 (Part 1 of 2). Patient Characteristics and Risk Factors

Variable	No. (%) of Patients[a] (*n* = 146)
Patient characteristics	
Sex, male	134 (92)
Age (years) (median and IQR)	55 (52–59)
Time since HIV diagnosis (years) (median and IQR)	15 (9–23)
At least 1 risk factor[b]	145 (99)
No. of risk factors (median and IQR)	3 (3–4)
Investigator-calculated FRAX score	
< 10% (low risk)	121 (83)
10%–20% (moderate risk)	20 (14)
> 20% (high risk)	5 (3)
Risk factors	
Body weight < 60 kg	
Yes	17 (12)
No	119 (82)
Not charted	10 (7)
Ethnicity White or Asian	
Yes	124 (85)
No	7 (5)
Not charted	15 (10)
History of fragility fracture	
Yes	18 (12)
No	6 (4)
Not charted	122 (84)
High risk of falls	
Yes	5 (3)
No	0 (0)
Not charted	141 (97)
Current smoker	
Yes	46 (32)
No	97 (66)
Not charted	3 (2)
Current alcohol use (> 3 units[c]/day)	
Yes	7 (5)
No	99 (68)
Not charted	40 (27)
Glucocorticoid use (> 5 mg prednisone or equivalent for > 3 months)	
Yes	6 (4)
No	140 (96)
Other medications with increased risk of osteoporosis[d]	
Yes	137 (94)
No	9 (6)
Comorbidities with increased risk of osteoporosis[e]	
Yes	80 (55)
No	66 (45)

TABLE 1 (Part 2 of 2). Patient Characteristics and Risk Factors

Variable	No. (%) of Patients[a] (*n* = 146)
Risk factors (continued)	
Malnourishment, as documented in chart notes	
Yes	14 (10)
No	0 (0)
Not charted	132 (90)
Inadequate calcium intake	
Yes	5 (3)
No	7 (5)
Not charted	134 (92)
Vitamin D deficiency	
Yes	3 (2)
No	1 (1)
Not charted	142 (97)
Postmenopausal (based on *n* = 12 women)	
Yes	3 (25)
No	0 (0)
Not charted	9 (75)
Premature menopause, as documented in chart notes (based on *n* = 12 women)	
Yes	0 (0)
No	2 (17)
Not charted	10 (83)
Antiretrovirals with increased risk of osteoporosis (at any time during study period)	
TDF only	30 (21)
PI only	32 (22)
TDF + PI	60 (41)
Not charted	24 (16)
CD4 nadir < 200 cells/μL	
Yes	64 (44)
No	45 (31)
Not charted	37 (25)
HIV-related neuropathy	
Yes	16 (11)
No	0 (0)
Not charted	130 (89)

IQR = interquartile range, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate.
[a]Except where indicated otherwise.
[b]Excluding age and HIV infection.
[c]1 unit of alcohol = 8–10 g of alcohol.
[d]TDF, medroxyprogesterone acetate, proton pump inhibitors, vitamin A supplements > 10 000 U/day, thiazolidinediones, antiandrogens, anticoagulants, anticonvulsants, aromatase inhibitors, chemotherapy, selective serotonin reuptake inhibitors, protease inhibitors, efavirenz, opioids, and diuretics.
[e]Chronic kidney disease, hepatitis B or hepatitis C, hypogonadism, hyperthyroidism, hyperparathyroidism, adrenal insufficiency, diabetes (type 1 or type 2), malabsorption disorder (celiac disease or inflammatory bowel disease), and rheumatoid arthritis.

the beginning of the study period, 2 patients had fewer than 2 yearly visits with a clinic physician, and 1 patient was not seeing a clinic physician. The included patients were mostly male (92%), their median age was 55 years, and HIV had been diagnosed a median of 15 years previously.

Patients had a median of 3 osteoporosis risk factors (in addition to age and HIV), and 145 patients (99%) had at least 1 risk factor. Risk factors that would be accounted for in a FRAX score calculation (previous fracture, parental hip fracture, current smoker, glucocorticoid use, rheumatoid arthritis, alcohol use 3 or more units daily [where 1 unit = 8–10 g alcohol]) were present for 21 patients. Risk factors and their frequencies are listed in Table 1.

A total of 39 patients (27%) underwent screening for osteoporosis during the study period. All screening at the clinic involved DXA ordered by a general practitioner or specialist physician. There was no documentation of patients screened through assessment without DXA or by use of a FRAX score. Among those who were screened, median age was 56 years, the median number of risk factors was 4, and 29 (74%) had TDF in their regimen (defined here and subsequently as TDF use at any time during the study period). Among the 107 patients who did not undergo screening, the median age was 54 years, the median number of risk factors was 3, and 61 (57%) had TDF in their regimen. The full breakdown of screening results is shown in Figure 1.

Overall, 25 patients in this study had osteoporosis (10 with prior diagnosis and 15 cases diagnosed during this study period). Among these patients with osteoporosis, the median age was 59 years and the median duration since HIV diagnosis was 18 years. Seventeen of these patients (68%) were receiving TDF. The investigator-calculated FRAX scores for patients with a diagnosis of osteoporosis were categorized as low risk (*n* = 13, 52%), moderate risk (*n* = 7, 28%), and high risk (*n* = 5, 20%). There were some slight differences in these characteristics for those who were screened and had normal BMD results. Among the 7 patients screened for osteoporosis who had normal BMD and the 13 patients with prior diagnosis of normal BMD, the median age was 54 years and the median duration since HIV diagnosis was 12 years. Nine (45%) of these 20 patients were receiving TDF. For the 7 patients screened for osteoporosis who had normal BMD, the investigator-calculated FRAX scores were categorized as low risk.

Among the 146 patients in our analysis, a total of 25 patients (17%) had osteoporosis at the end of the study period. Among patients with a diagnosis of osteoporosis (either previously or during this study period), 15 (60%) were treated with a bisphosphonate, 4 were treated with vitamin D or calcium supplementation only, and 6 were not given any treatment. Among patients not receiving treatment, there was no documentation of bisphosphonate contraindication. Denosumab treatment was not documented for any patients in this study. Twenty-two of the

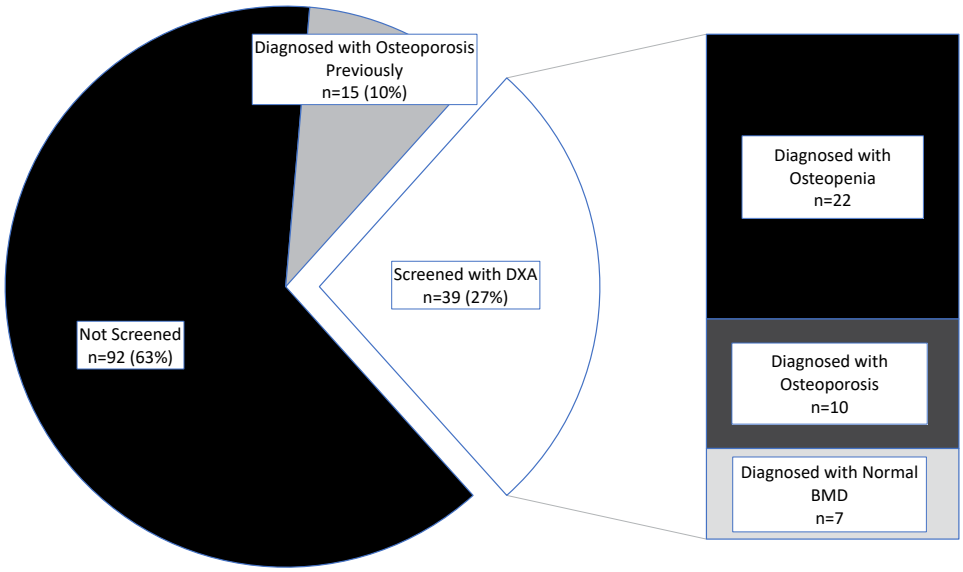

FIGURE 1. Screening and diagnosis of osteoporosis.

patients with osteoporosis were receiving an ART regimen associated with risk of decreased BMD: 5 were receiving a protease inhibitor without TDF, 5 were receiving TDF without a protease inhibitor, and 12 were receiving both TDF and a protease inhibitor concurrently. For 10 of the 17 patients (59%) who were receiving TDF, the TDF was changed to another ART for reasons of bone health.

Various nutritional interventions were recommended for patients with and without osteoporosis: calcium supplementation for 32 patients (22%) and vitamin D supplementation for 46 patients (32%). TDF alone was discontinued or substituted for another ART in 13 patients (9% of the total sample) for reasons of bone health. Also for the purpose of bone health, 1 patient was switched off an ART regimen consisting of TDF and a protease inhibitor. None of the patients who were receiving an ART regimen that included a protease inhibitor without TDF had the protease inhibitor discontinued for reasons of bone health. The multidisciplinary team was involved in management of bone health for 57 patients (39%) with or without osteoporosis: pharmacists (n = 38), nurses (n = 21), and dieticians (n = 14). Additional results for interventions made are shown in Table 2.

DISCUSSION

This study has showcased the high frequency of risk factors for osteoporosis among people living with HIV, has highlighted that screening is not routinely documented in many cases, and has shown that suitable treatment modalities may be underutilized. These problems may be common in primary care clinics that serve people living with HIV, as similar findings were reported in a study conducted in the United Kingdom.[18] The investigators in that study found that within their sample of 20 people living with HIV who were at least 50 years of age, only 3 (15%) were assessed by DXA, and none had had a FRAX score calculated in the previous 3 years. Our study can serve as a prompt for local improvement in the management of osteoporosis and as a call for other clinics to evaluate their practices.

Osteoporosis is prevalent in the HIV population, and identifying and addressing risk factors for this condition are important, given data showing a higher prevalence of traditional risk factors among those with HIV.[19] We looked at a comprehensive list of risk factors and found a median of 3 osteoporosis risk factors (in addition to age and HIV). These included risk factors, such as use of selective serotonin reuptake inhibitors, beyond those captured in risk

TABLE 2. Treatments and Recommendations for Osteoporosis for All Patients

Treatment or Recommendation	No. (%) of Patients (n = 146)
Bisphosphonate	16 (11)
Calcium	
Supplements	32 (22)
Dietary	12 (8)
Vitamin D supplements	46 (32)
Smoking cessation	50 (34)
Weight-bearing exercises	11 (8)
Decrease alcohol intake	1 (1)
ART adjustment for bone health	
TDF discontinued	13 (9)
TDF and PI discontinued	1 (1)

ART = antiretroviral therapy, PI = protease inhibitor, TDF = tenofovir disoproxil fumarate.

calculators such as FRAX, which may partly explain why fracture risk is often underestimated by these risk calculators. In addition, there is a chance that risk factors were underdocumented, especially for women. For example, there was no documentation concerning menopause for 9 of the 12 women included in this study, despite evidence showing that early menopause can double the risk of fractures.[20]

Despite the presence of multiple risk factors, only 27% of the patients were screened for osteoporosis. DXA was the preferred screening tool for all of these patients. The FRAX scores calculated by investigators during the course of this study showed that 17% of patients were at moderate or high risk of fractures, which is on par with the literature,[3] but there was high discordance among the scores. For example, for 52% of those in whom osteoporosis was diagnosed (previously or during this study) by DXA, the investigator-calculated FRAX score was "low risk". Studies have shown that relying on FRAX as an independent risk assessment tool may lead to underdetection of patients who may be at risk for osteoporosis and who may be candidates for treatment,[21,22] Applying the results of our study, it may be appropriate to recommend DXA for patients who, despite having a low FRAX score, may have numerous other risk factors for osteoporosis. We suspect that osteoporosis rates might have been higher than we observed, given the large number of patients in this study who were not screened.

For people living with HIV, treatment with bisphosphonates has been shown to significantly improve BMD while being well tolerated.[23] However, bisphosphonates were being taken by only 11% of our population (15 patients with osteoporosis and 1 patient with osteopenia), despite 17% having a diagnosis of osteoporosis. There is a possibility that patients in our study were not offered bisphosphonates because of contraindications (e.g., renal insufficiency, cost concerns), but if so, there was no supporting documentation. Current guidelines recommend bisphosphonate for people living with HIV according to the same criteria as used for the general population, but this recommendation does not take into account the potential underestimation of fracture risk by FRAX and BMD in this population.[24]

In our study, only 22% of patients were receiving calcium supplementation, and only 32% were receiving vitamin D supplementation, despite the presence of numerous risk factors for osteoporosis, including 84% of patients receiving an ART regimen that included TDF or a protease inhibitor (or both). Calcium and vitamin D, known as crucial nutrients for optimal bone health, have been explored for their preventive role in bone health for patients who are taking ART regimens containing TDF, a medication that affects BMD. One study compared ART-naive HIV-infected patients who were taking vitamin D 4000 units daily and calcium carbonate 500 mg twice daily with patients who were taking placebo; the intervention group had a lesser decline in total hip BMD and lower markers for bone turnover over 48 weeks.[25] There were no clear differences with regard to adverse events in the treatment and placebo groups. These results, albeit weak, suggest another possible intervention for preventing osteoporosis. These 2 supplements are relatively inexpensive, easy to take, and generally well tolerated. It may be appropriate to recommend vitamin D and calcium supplementation for all patients with HIV who have risk factors for osteoporosis.

Few patients in our study population were switched from TDF to another ART for reasons of bone health. Given the association of TDF and protease inhibitors with decreased BMD and fractures, people with osteopenia or osteoporosis who are taking these medications should have a discussion with their health care provider about alternative ART.[4] Although it is common to modify regimens containing TDF or protease inhibitors and to consider alternatives,[26,27] there are clinical scenarios in which a switch may not be possible. Data from ART switch studies are limited to surrogate markers such as DXA and bone turnover markers; there are currently no clinical data to suggest that discontinuing TDF (or other ART with negative bone effects) will reduce fracture risk over time.[28] Additionally, there are many third-agent alternatives that can be used to replace protease inhibitors but fewer options for TDF. However, despite the conflicting evidence, this is still a potential avenue worthy of exploration. Alternatives to TDF include abacavir and tenofovir alafenamide, but both of these options have limitations. Abacavir may not be suitable for some patients because of resistance or the presence of the HLA-B*5701 allele marker for hypersensitivity.[29] Tenofovir alafenamide is attractive because of its improved safety profile for kidney function and BMD with equivalent efficacy; however, its use may be limited by a variety of issues, including drug coverage, increases in serum lipids, weight gain, and limited data on long-term efficacy and safety.[28,30-32] An additional strategy to optimize ART for bone health is to use a 2-drug regimen such as dolutegravir with lamivudine or dolutegravir with rilpivirine, both of which are available in Canada as coformulated, fixed-dose combination tablets. This option is limited to patients with virologic suppression, no history of virologic failure, no resistance to either agent in the 2-drug regimen, and no hepatitis B co-infection.[33,34]

Maximizing use of the multidisciplinary team can help to comprehensively address issues associated with osteoporosis. Studies have shown that involving allied health professionals, such as dieticians and nurses, in screening for chronic disease in primary care clinics can improve the identification of patients with modifiable comorbidities.[18] Pharmacists can be instrumental in screening people who have or are at risk of major diseases, such as cardiovascular disease, certain cancers, and osteoporosis.[35] This type of practice, specifically for osteoporosis, has been successfully implemented in community pharmacies.[36] Although

HIV teams traditionally focus on HIV and its manifestations, it is important for all team members to address the chronic diseases associated with HIV, given this population's increasing age.

This study had several limitations. First, patients younger than 50 years of age were not included. These patients may have been underscreened or undertreated and might benefit from earlier intervention for bone health. Second, given the retrospective design, there is the possibility of underdocumentation of interventions such as screening or treatment, leading to inaccurate conclusions. Third, given the single-centre design, there may be limited generalizability to populations outside our clinic.

CONCLUSION

This study has highlighted an area for practice improvement in HIV care. Patients over age 50 at the John Ruedy Clinic had risk factors for osteoporosis that warranted screening, yet rates of screening were low. At the same time, rates of osteoporosis were high, and interventions were underutilized. An opportunity exists to improve care for these patients, by increasing screening with DXA, making proactive recommendations for lifestyle measures and intake of calcium and vitamin D, and selecting bone-friendly ART. Further study on the use of the multidisciplinary team to achieve this improvement in care is needed.

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Risk of Neutropenia in Adults Treated with Piperacillin–Tazobactam or Cefazolin: A Retrospective Cohort Study

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ABSTRACT

Background: Neutropenia is an adverse effect associated with the use of several antibiotics, including piperacillin–tazobactam (P/T). Previous findings have suggested that the risk of neutropenia in children is significantly higher with P/T than with ticarcillin–clavulanate.

Objectives: To compare the risk of neutropenia associated with P/T and with cefazolin in an adult population and to describe the characteristics of neutropenia episodes observed.

Methods: This descriptive retrospective study involved patients aged 18 years or older who received a minimum of 10 days of treatment with P/T or cefazolin between January 2009 and December 2013. Patients who experienced neutropenia (absolute neutrophil count $< 1.5 \times 10^9$/L) were compared, using univariate and multivariate logistic regression models, between those who received P/T and those who received cefazolin.

Results: A total of 207 patients were included (104 who received P/T and 103 who received cefazolin). Ten episodes of neutropenia were observed, 5 with each antibiotic (4.8% and 4.9%, respectively; odds ratio 0.99, 95% confidence interval 0.278–3.527). The mean cumulative dose of piperacillin was 290.4 g among patients who experienced neutropenia and 247.0 g among all patients treated with P/T, and the mean treatment duration was 24.0 days and 21.0 days, respectively. The average time before the onset of neutropenia was slightly longer with P/T than with cefazolin (22.0 versus 17.2 days, $p = 0.38$).

Conclusions: Although these results require confirmation in a larger clinical trial (to lessen possible attribution bias), the risk of neutropenia appeared to be similar between P/T and cefazolin.

Keywords: neutropenia, piperacillin–tazobactam, cefazolin

RÉSUMÉ

Contexte : La neutropénie est un effet indésirable associé à l'utilisation de plusieurs antibiotiques, dont la pipéracilline-tazobactam (P/T). Des données récentes indiquent que le risque de neutropénie chez les enfants est significativement plus élevé avec la P/T qu'avec l'association ticarcilline-clavulanate.

Objectifs : Comparer le risque de neutropénie associé à la P/T et à la céfazoline chez une population adulte et décrire les caractéristiques des épisodes de neutropénie observés.

Méthodes : Cette étude rétrospective descriptive impliquait des patients âgés d'au moins 18 ans ayant reçu un traitement d'au moins 10 jours par P/T ou céfazoline entre janvier 2009 et décembre 2013. Les patients ayant présenté une neutropénie (nombre absolu de neutrophiles $< 1,5 \times 10^9$/L) ont été comparés, à l'aide de modèles de régression logistique univariée et multivariée, entre ceux qui ont reçu de la P/T et ceux qui ont reçu de la céfazoline.

Résultats : Au total, 207 patients ont été inclus (104 ayant reçu de la P/T et 103 ayant reçu de la céfazoline). Dix épisodes de neutropénie ont été observés, 5 avec chaque antibiotique (4,8 % et 4,9 %, respectivement; rapport des cotes 0,99; intervalle de confiance à 95 % 0,278-3,527). La dose cumulée moyenne de pipéracilline était de 290,4 g chez les patients ayant présenté une neutropénie et de 247,0 g chez tous les patients traités par P/T. La durée moyenne du traitement était de 24,0 jours et 21,0 jours, respectivement. Le délai moyen avant l'apparition de la neutropénie était légèrement plus long avec la P/T qu'avec la céfazoline (22,0 contre 17,2 jours, $p = 0,38$).

Conclusions : Bien que ces résultats nécessitent une confirmation dans un essai clinique de plus grande envergure (afin de réduire d'éventuels biais d'attribution), le risque de neutropénie semble être similaire chez les personnes ayant reçu de la P/T et ceux ayant reçu de la céfazoline.

Mots-clés : neutropénie, pipéracilline-tazobactam, céfazoline

INTRODUCTION

Hematologic toxic effects are well-known side effects of several drugs, including multiple classes of antimicrobials. β-Lactam antibiotics are particularly implicated and are among the most commonly used antimicrobials known to cause agranulocytosis.[1,2] The pathophysiology of β-lactam–associated neutropenia remains poorly defined and only a few case reports and literature reviews have been published on the subject; notably, no randomized studies regarding the risk of neutropenia secondary to piperacillin–tazobactam (P/T) relative to other antibiotics have been published.[3-6]

Antibiotic-associated neutropenia is characterized by a decline, either sudden or gradual, in circulating neutrophils. There is no consensual definition for drug-induced neutropenia, but it has been previously defined as an absolute neutrophil count below 1.0 or 2.0×10^9/L for β-lactam antibiotics.[6-9] Among other factors, increasing cumulative exposure to β-lactams has been linked to increases in the occurrence of neutropenia.[3,6]

An initial study conducted in our centre in 2012 established that there was a significantly higher risk of neutropenia among children who received P/T than among those who received ticarcillin–clavulanate.[10] We wanted to confirm whether the higher risk of P/T-associated neutropenia was also present for adults. When we started the current study (with data collection beginning in 2009), ticarcillin–clavulanate was unavailable (on long-term back order). Since then, in 2015, the sole manufacturer of ticarcillin–clavulanate ceased production in North America. As such, for the adult study, we could not use the same comparator drug as was used in the pediatric study.[10] In terms of a substitute comparator, few β-lactam antibiotics are used on a regular basis, for relatively long periods, at daily doses comparable to those of piperacillin. Cloxacillin would be one example, as it is typically used in amounts between 8 and 12 g daily; however, it was seldom used in our centre. We therefore selected cefazolin, a parenteral β-lactam that is often used on a long-term basis, as the comparator, although the usual daily doses were predictably lower with cefazolin (6 g/day) than with P/T (12 g/day).

The primary objective of this study was to compare the proportions of cases of neutropenia observed during treatment with P/T or cefazolin in adult patients. The secondary objectives were to compare the following variables in the 2 groups: duration of antibiotic therapy before occurrence of neutropenia, cumulative dose of each antibiotic, presence of confounding variables (age, sex, concurrent drug use), duration of neutropenia, and neutrophil recovery time.

METHODS

This retrospective cohort study was conducted in a university teaching medical centre in Quebec City, Quebec. Cefazolin was chosen as the comparator drug for practical reasons, as outlined in the Introduction. Like P/T, this drug is widely used in practice for infections requiring prolonged courses of treatment in adults.

The medical records of patients 18 years of age or older who had received at least 10 days of treatment with P/T or cefazolin between January 2, 2009, and December 3, 2013, were reviewed. The minimum of 10 days of exposure was selected because the time to onset of neutropenia associated with β-lactam antibiotics was previously estimated at 10–15 days.[3,9-11] Potential participants were identified through a list of patients who received P/T or cefazolin, generated by the hospital pharmacy software. Patients were excluded if other antimicrobials had been administered in the week preceding prescription of P/T or cefazolin. Also excluded were patients with immunosuppression, those undergoing treatment for active malignancy (according to the list of antineoplastic drugs shown in Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209), HIV infection, neutropenia at the start of treatment with P/T or cefazolin, or congenital abnormalities associated with the development of neutropenia. Patients treated concomitantly with drugs known to cause neutropenia (see Appendix 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209), such as carbamazepine or antithyroid drugs, were not excluded, but the concomitant use of these drugs was taken into account in the analyses.[2,11,12]

Episodes of neutropenia were defined by the first value of absolute neutrophil count less than 1.5×10^9/L observed after initiation of P/T or cefazolin until the end of the studied episode of care. The time to recovery was defined by the date when absolute neutrophil count greater than 1.5×10^9/L was first reported following the original decline.

Quantitative variables are reported as means with standard deviations (SDs) or medians with interquartile ranges and ranges, and qualitative variables are reported as frequencies with percentages. Bivariate analyses were performed using Wilcoxon Mann–Whitney tests, Student *t* tests after normality verification, and χ^2 or Fisher exact tests as appropriate. Crude and adjusted odds ratios (ORs) were estimated by univariate and multivariate logistic regression models. The goodness of fit of the logistic models was checked by the Hosmer and Lemeshow test. All statistical analyses were performed using SPSS 24 statistics software (IBM Corporation) and SAS 9.4 statistics software (SAS Institute) with 2-sided significance level set at $p < 0.05$.

This study was approved by the clinical research ethics review board of the CHU de Québec – Université Laval (approval number GU14-166 AQUEM 2013-11).

RESULTS

A total of 583 medical records were identified in which P/T or cefazolin was documented as the first antibiotic administered. A total of 207 records met the inclusion criteria and were included in the analysis. The primary reasons for exclusion of the remaining 376 records were treatment duration less than 10 days and unavailability of the medical record at the time of data collection (n = 237, 63.0%), administration of another antibiotic within the 7 days preceding the prescription of P/T or cefazolin (n = 102, 27.1%), use of immunosuppressive drugs (n = 16, 4.3%; see Appendix 3, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209, for a list of the immunosuppressive drugs used for these exclusions), and neoplasia or active chemotherapy (n = 21, 5.6%).

Among the 207 patients who met the inclusion criteria, 104 (50.2%) were in the P/T group and 103 (49.8%) in the cefazolin group. Table 1 summarizes patients' characteristics according to the antibiotic received. Patients in the P/T group were older and there was a lower proportion of men relative to the cefazolin group (p = 0.001 for both). In addition, patients in the P/T group had, on average, a higher baseline neutrophil count (10.5 × 10^9/L versus 7.6 × 10^9/L, respectively; $p < 0.001$) and shorter duration of treatment (median 17 versus 20 days, respectively; p = 0.058). The mean cumulative dose in the P/T group was 247.0 (SD 145.0) g. Cefazolin was given primarily for skin and skin structure infections and for bone and joint infections (n = 84/103, 81.6%). P/T was given for a greater variety of indications (Table 1).

Ten episodes of neutropenia were observed, 5 in each group (4.8% in the P/T group, 4.9% in the cefazolin group). The unadjusted logistic regression model showed no difference in the risk of neutropenia, whether patients received P/T or cefazolin (OR 0.99, 95% confidence interval 0.278–3.527; p = 0.99). This difference remained statistically nonsignificant after adjustment for age, sex, baseline neutrophil count, and presence of concomitant treatments. However, the 10 patients who experienced neutropenia were younger than those without neutropenia (mean age 49 [SD 14] years, range 33–74 years, versus 60 [SD 17] years, range 21–94 years; p = 0.042).

Table 2 summarizes the characteristics of the patients who experienced neutropenia. The neutropenia occurred in the P/T group after a mean cumulative dose of 290.4 g, which was slightly higher than the average dose administered in this group as a whole (247.0 g), but the difference was not statistically significant. The mean cumulative dose recorded for cefazolin among patients who experienced neutropenia was 145.2 g, less than the mean cumulative dose of P/T for patients with neutropenia (290.4 g), but similar to the mean dose within the cefazolin group overall (149.0 g).

The mean time to onset of neutropenia and the neutrophil baseline value were slightly higher in the P/T group than in the cefazolin group, although these

TABLE 1. Patient Characteristics

Characteristic	Study Group; No. (%) of Patients[a]		p Value[b]
	Piperacillin–Tazobactam (n = 104)	Cefazolin (n = 103)	
Age (years) (mean ± SD)	63.0 ± 16.8	55.0 ± 15.8	0.001
Sex (male)	44 (42.3)	68 (66.0)	0.001
Initial ANC (× 10^9/L) (mean ± SD)	10.5 ± 5.5	7.6 ± 3.9	< 0.001
Cumulative dose[c] (g) (mean ± SD)	247.0 ± 145.0	149.0 ± 83.3	< 0.001
Treatment duration (days)			
Mean ± SD	21.0 ± 14.2	23.0 ± 10.8	0.39
Median (IQR)	17.0 (13.5–24.5)	20.0 (15.0–29.0)	0.058
Occurrence of neutropenia	5 (4.8)	5 (4.9)	> 0.99
Concomitant treatment			
Phenytoin	1 (1.0)	0	
Corticosteroids	3 (2.9)	5 (4.9)	
Cotrimoxazole	1 (1.0)	0	
Sulfasalazine	0	1 (1.0)	
Clozapine	2 (1.9)	0	
β-Lactam drugs[d]	3 (2.9)	5 (4.9)	
Indication[e]			
SSS, bone, or joint infection	22 (21.2)	84 (81.6)	
Intra-abdominal infection	48 (46.2)	0	
Pulmonary infection	8 (7.7)	0	
Urinary tract infection	2 (1.9)	0	
ENT infection	1 (1.0)	2 (1.9)	
Other	24 (23.1)	17 (16.5)	

ANC = absolute neutrophil count; ENT = ear, nose, and throat; IQR = interquartile range; SD = standard deviation; SSS = skin and skin structure.
[a]Except where indicated otherwise.
[b]Statistical significance defined as $p \leq 0.05$.
[c]Expressed as grams of piperacillin content.
[d]β-Lactam drugs other than piperacillin–tazobactam or cefazolin that should be administered after treatment initiation with cefazolin or piperacillin–tazobactam.
[e]A patient could have been treated for more than one indication.

TABLE 2. Characteristics of Episodes of Neutropenia (n = 10 Patients)

Case No.	Sex	Age (years)	Indication for Antibiotic	Treatment Duration (days)	Cumulative Dose[a] (g)	Time to Onset (days)	Initial ANC (× 10^9/L)	Nadir of Neutrophils (× 10^9/L)	Recovery Time[b] (days)
Piperacillin–tazobactam									
1	M	50	Wound infection	19	228	19	14.2	1.4	NA
2	F	36	Suppurated adenopathy	18	216	18	11.1	0.9	2
3	F	33	Intra-abdominal infection	41	492	33	5.7	0.9	7
4	F	74	Abscess	21	252	20	19.9	1.0	4
5	F	60	Diverticulitis and abscess	22	264	20	8.0	1.1	3
Mean ± SD[c]	20% M	50.6 ± 17.0	NA	24.2 ± 9.5	290.4 ± 114.2	22.0 ± 6.2	11.8 ± 5.6	1.1 ± 0.2	4.0 ± 2.1
Cefazolin									
6	F	63	Ear chondritis	26	156	26	3.1	1.4	10
7	M	55	Cellulitis	26	156	19	9.5	1.3	4
8	M	41	Prosthetic material infection	27	162	26	8.5	0.8	1
9	F	45	Cellulitis	12	72	12	2.2	1.1	16
10	F	33	Necrotizing fasciitis	30	180	3	11.6	1.4	12
Mean ± SD[c]	40% M	47.4 ± 11.8	NA	24.2 ± 7.0	145.2 ± 42.0	17.2 ± 9.8	7.0 ± 4.0	1.2 ± 0.3	8.6 ± 6.0
p value[d]	> 0.99	0.74		> 0.99	–	0.38	0.16	0.49	0.20

ANC = absolute neutrophil count, F = female, NA = not available or not applicable, M = male, SD = standard deviation.
[a]Cumulative dose of the antibiotic at the time when criteria for neutropenia were met.
[b]Bone marrow recovery time, defined as the time to achieve ANC > 1.0 × 10^9/L.
[c]Except where indicated otherwise.
[d]For comparison between P/T and CFZ groups.

differences were not statistically significant (time to onset 22.0 days versus 17.2 days, respectively, $p = 0.38$; 11.8 × 10^9/L versus 7.0 × 10^9/L, respectively, $p = 0.16$). The neutrophil nadir was similar for the 2 antibiotics (1.1 × 10^9/L in the P/T group and 1.2 × 10^9/L in the cefazolin group; $p = 0.49$). Finally, the mean time for the bone marrow to recover after the antibiotics were stopped was twice as long in the cefazolin group as in the P/T group (8.6 days versus 4.0 days, respectively; $p = 0.20$); the absence of statistical significance may have been related to the small sample sizes.

DISCUSSION

In this study, the prevalence of neutropenia was similar between patients who received P/T and those who received cefazolin (4.8% and 4.9%, respectively), which suggests that the risk of this adverse effect was also similar in the 2 groups. In 2 small studies published in the 1990s, the prevalence of neutropenia induced by P/T was between 1% and 4%, similar to the prevalence observed in the present study.[13,14] A systematic review of case reports, retrospective cohort studies, and clinical trials describing neutropenia associated with piperacillin and P/T was published in 2007.[6] This review showed that the prevalence of neutropenia associated with piperacillin or P/T was less than 1%, but the authors stated that the true prevalence of piperacillin- or P/T-associated neutropenia was unknown.[6] Similarly, the prevalence of cefazolin-associated neutropenia is not well defined and is mostly based on observational cohort studies. The prevalence of neutropenia in patients treated with cefazolin has been reported between 1.3% and 3.3%, which is slightly lower than what we observed.[15-18] Table 3 summarizes the results of previous studies describing neutropenia associated with P/T and cefazolin.

The criteria for defining neutropenia strongly influence the reported rates of β-lactam–associated neutropenia. For

TABLE 3. Summary of Studies of Neutropenia Associated with Piperacillin–Tazobactam and Cefazolin in Adults

Reference, Grouped by Antibiotic	Study Design	No. of Patients	Definition of Neutropenia ($\times 10^9$/L)	Mean Cumulative Dose (g)[a]	Delay to Onset of Neutropenia (days)	Prevalence of Neutropenia (%)
Piperacillin–tazobactam (P/T)						
Peralta et al. (2003)[8]	Case series	43	2.0	330	26.8	34
Uzun et al. (2013)[3]	Case report	1	0.5	204	17.0	NR
Lang et al. (1991)[13]	Case series	6	2.0	144–750	16.0	33
Ruiz-Irastorza et al. (1996)[14]	Case report	1	0.5	240	17.0	NR
Current study	Retrospective analysis	104 (P/T group)	1.5	290	22.0	4.8
Cefazolin (CFZ)						
Youngster et al. (2014)[16]	Retrospective cohort study	119	1.0	NR	NS	3.3
Turner et al. (2018)[17]	Retrospective cohort study	180	1.5	204	20[b]	2.7
Smith (1982)[18]	Prospective study	149	NR	NR	NR	1.3
Lee et al. (2015)[15]	Retrospective cohort study	38	1.5	NR	NR	2.6
Current study	Retrospective analysis	103 (CFZ group)	1.5	145	17.2	4.9

NR = not reported.
[a]Expressed as grams of piperacillin content.
[b]Median value.

instance, Scheetz and others[6] defined neutropenia as absolute neutrophil count less than 0.5×10^9/L, which is much more stringent than the definitions used by other authors (e.g., $\leq 2.0 \times 10^9$/L).[8,13] The use of this criterion may have led Scheetz and others[6] to underestimate the rate of neutropenia. We deliberately selected a cut-off of 1.5×10^9/L, halfway between the definition often used in clinical practice (1.0×10^9/L) and the definition selected in most studies (2.0×10^9/L).[8,13] When we performed the same statistical analyses with a different definition of neutropenia (absolute neutrophil count $< 1.0 \times 10^9$/L), the prevalence of antibiotic-associated neutropenia with the 2 antibiotics was predictably lower, but still not significantly different (1.9% [2/104] for P/T versus 1.0% [1/103] for cefazolin). Similar results were obtained when neutropenia was defined as an absolute neutrophil count below 2.0×10^9/L (7.7% [8/104] for P/T versus 5.8% [6/103] for cefazolin).

Increased cumulative exposure to β-lactams has been linked to increases in the occurrence of neutropenia. A retrospective cohort study published in 2003 reported the occurrence of neutropenia at a threshold cumulative dose of P/T between 204 and 612 g.[8] Patients treated with piperacillin who experienced neutropenia received an average cumulative dose of 330 g, whereas the average cumulative dose was lower, at 237 g, in the non-neutropenic group. In that previous study, neutropenia was defined by a neutrophil count of 2.0×10^9/L or less. In our study, the cumulative dose of P/T was only slightly higher among patients who experienced neutropenia than among those who did not experience neutropenia (290.4 g versus 244.8 g; difference not significant). This value is similar to the cumulative dose (284 g) described for an episode of neutropenia associated with the use of piperacillin in a young man after 21 days of treatment.[19] Unsurprisingly, the cumulative dose of cefazolin was lower than that of P/T, which reflects the respective dosing schedules of these medications.

The defined daily dose (DDD) represents another way to appreciate the magnitude of antibiotic use. The DDD, a benchmarking tool developed by the World Health Organization (www.whocc.no), represents the assumed average daily maintenance dose for a drug when used for its main indication in adults. However, the DDD does not always reflect precisely the recommended or prescribed daily dose. For instance, the DDD for cefazolin is 3 g, whereas in our institution cefazolin is seldom prescribed at less than 6 g/day. Conversely, the DDD for piperacillin is 14 g, which reflects more accurately its usual dosing range, between 12 and 16 g/day. The mean amounts of antibiotic administered to patients who experienced neutropenia were 20.7 DDD for piperacillin and 48.3 DDD for cefazolin. However, if 6 g/day is used to represent the usual maintenance dose of cefazolin, rather than 3 g/day, patients in the cefazolin group received an average of 24.2 DDD, which would be comparable to the DDD for piperacillin. To date, no clear threshold

cumulative dose leading to neutropenia has been identified for β-lactam antibiotics, and to our knowledge no study has examined this issue from the perspective of DDDs.

Ceftaroline, a fourth-generation cephalosporin active against methicillin-resistant *Staphylococcus aureus*, has recently been associated with an increased risk of neutropenia, relative to other commonly used antistaphylococcal antibiotics, such as cefazolin, nafcillin, and vancomycin.[17] In that cohort study, cumulative dose and duration of exposure were not significant predictors of neutropenia, whereas age, baseline absolute neutrophil count, presence of a bone and joint infection, and use of ceftaroline were significantly associated with neutropenia.[17]

Neutropenia is an uncommon side effect of β-lactam therapy and usually requires more than 10 days of exposure to the antibiotic.[1,6,16] In our study, the time to onset of neutropenia observed in the P/T group (mean 22.0 days, median 20 days, IQR 19–20 days) was slightly longer than values previously reported.[3,15] For cefazolin, the observed time to onset was shorter (mean 17.2 days, median 19 days, IQR 12–26 days) and similar to the value reported in a retrospective cohort study.[17] The bone marrow recovery time after β-lactam–induced neutropenia is reported to be about 7 days,[3,4,6,8,9,19] and Peralta and others[8] reported an average recovery time of 3.8 days. This is in line with our observations for the P/T group (bone marrow recovery after a mean of 4.0 [SD 2.1] days). Mean bone marrow recovery time was longer for cefazolin (8.6 [SD 6.0] days), although the difference was not statistically significant ($p = 0.20$).

Two mechanisms have been proposed to explain β-lactam–associated neutropenia. The first suggests an immunological phenomenon as the cause of the decrease in neutrophils. Circulating immunoglobulin G (IgG) directed against neutrophils was found in several patients who had been exposed to β-lactams and P/T.[9] The IgG reacts with granulocytes and platelets.[6,18,19] Such an immunological hypothesis could explain in part the fact that "cross-neutropenia" is possible between β-lactam antibiotics.[19,20] The second hypothesis concerns a direct toxic effect of the antibiotic on the bone marrow, thereby hindering granulopoiesis.[19,20]

The diversity in the infectious diseases observed in our study reflects the clinical usefulness and spectrum of antibacterial activity of both P/T and cefazolin. As might be expected, cefazolin was used mainly for treatment of skin, skin structure, and osteo-articular infections, whereas P/T, which displays a broader antibacterial spectrum, was used for a greater variety of situations, particularly for polymicrobial infections. However, the types of infections for which the patients were treated were so varied that we were unable to establish any association with the outcome (Table 2). Some potential confounding factors such as age, sex, and initial absolute neutrophil count were significantly different between the 2 groups. Therefore, we fitted a multivariate model with adjustment for these factors. However, the results of adjusted and crude models evaluating neutropenia in both the P/T and cefazolin groups were very similar.

Our study had some limitations, mainly because of the retrospective nature of the study design. In particular, the data were dependent on the time when white blood cell count was determined, which varied greatly depending on the length of stay and whether the treatment was administered on an outpatient basis. This limitation has a potential influence on the estimation of time to recovery from neutropenia. Finally, the small sample size limited the possibility of detecting a meaningful difference in the risk of neutropenia between the 2 antibiotics.

CONCLUSION

The results of this study suggest a comparable risk of neutropenia after 10 days of treatment with P/T or cefazolin. The risk observed here was lower than that reported in the literature, at least for an adult population. Neutropenia associated with β-lactam antibiotics remains a poorly documented adverse effect. Further studies are needed to better establish the individual risk for each antibiotic, as well as other contributing factors, such as the cumulative dose.

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TLC-Act: A Novel Tool for Managing Drug Interactions

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ABSTRACT

Background: Clinical decision support systems (CDSS) are used by pharmacists to assist in managing drug–drug interactions (DDIs). However, previous research suggests that such systems may perform suboptimally in providing clinically relevant information in practice.

Objectives: The primary objective of this study was to develop a novel DDI management tool to reflect the clinical thought process that a pharmacist uses when assessing a DDI. The secondary objective was to investigate practitioners' perceptions of this tool.

Methods: This study was conducted in 3 phases: development of the DDI management tool, implementation of the tool in clinical practice, and collection of practitioners' opinions of the tool through an online qualitative survey (although because of circumstances related to the COVID-19 pandemic, the study population for the survey phase included only pharmacy residents). A comprehensive literature search and analysis by an expert panel provided underlying context for the DDI management tool. The tool was validated through simulation against a known list of DDIs before implementation into practice by hospital pharmacists and pharmacy residents. Participating pharmacy residents were invited to provide feedback on the tool. Survey results were analyzed using descriptive statistics.

Results: The novel tool that was developed in this study (called TLC-Act) consisted of components important to a pharmacist when assessing a DDI, including the duration of concomitant use of the interacting medications and patient-specific risk factors. Study participants implemented the tool in clinical practice for a total of 6 weeks. Of the 28 pharmacy residents surveyed, 15 (54%) submitted a response, of whom 11 (73%) found the TLC-Act tool to be slightly more useful for assessing a DDI than usual care with the CDSS alone.

Conclusions: The TLC-Act tool maps out a pharmacist's clinical thought process when assessing a DDI in practice. This novel tool may be more useful than a CDSS alone for managing DDIs, as it takes into account other important factors pertinent to the assessment of a DDI.

Keywords: drug interactions, algorithm, tool, pharmacists, resident, hospital

Note: This article contains supplementary material (Supplement 1), available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209

RÉSUMÉ

Contexte : Les systèmes d'aide à la décision clinique (SADC) sont utilisés par les pharmaciens pour les aider à gérer les interactions médicamenteuses (IM). Cependant, des recherches antérieures indiquent que ces systèmes peuvent fonctionner de manière sous-optimale pour fournir des informations cliniquement pertinentes dans la pratique.

Objectifs : L'objectif principal de cette étude consistait à développer un nouvel outil de gestion des IM pour reproduire le processus de réflexion clinique adopté par un pharmacien quand il les évalue. L'objectif secondaire consistait, quant à lui, à enquêter sur les perceptions des praticiens à l'égard de cet outil.

Méthodes : Cette étude a été menée en 3 phases : développement de l'outil de gestion des IM; sa mise en place dans la pratique clinique; et recueil des avis des praticiens sur celui-ci au moyen d'une enquête qualitative en ligne (bien qu'en raison des circonstances liées à la pandémie de COVID-19, la population étudiée pour la phase de l'enquête ne comprenne que des résidents en pharmacie). Une recherche documentaire et une analyse approfondies effectuées par un groupe d'experts ont fourni le contexte sous-jacent de l'outil de gestion des IM. L'outil a été validé par simulation par rapport à une liste connue d'IM avant sa mise en pratique par les pharmaciens hospitaliers et les résidents en pharmacie. Les résidents en pharmacie qui participaient à l'étude ont été invités à donner leur avis sur l'outil. Les résultats de l'enquête ont été analysés à l'aide de statistiques descriptives.

Résultats : Le nouvel outil développé dans le cadre de cette étude (le « TLC-Act ») se composait d'éléments d'évaluation des IM importants pour un pharmacien, y compris la durée de l'utilisation concomitante des médicaments en interaction et les facteurs de risque propres au patient. Les participants à l'étude ont mis en œuvre l'outil dans la pratique clinique pendant un total de 6 semaines. Sur les 28 résidents en pharmacie interrogés, 15 (54 %) ont soumis une réponse, et 11 (73 %) d'entre eux ont trouvé que l'outil TLC-Act était légèrement plus utile pour évaluer les IM que le SADC seul utilisé habituellement.

Conclusions : L'outil TLC-Act cherche à reproduire le processus de réflexion clinique d'un pharmacien lorsqu'il évalue les IM dans la pratique. Ce nouvel outil peut être plus utile qu'un SADC utilisé seul pour gérer les IM, car il prend en compte d'autres facteurs importants qui sont pertinents pour leur évaluation.

Mots-clés : interactions médicamenteuses, algorithme, outil, pharmaciens, résident, hôpital

INTRODUCTION

Pharmacists are responsible for identifying and assessing drug–drug interactions (DDIs); however, the sheer volume of potential interactions requires a degree of reliance on computer systems, which have their own limitations. A DDI occurs when one drug changes the pharmacokinetic or pharmacodynamic properties of another drug, resulting in alterations in physiological processes or activity.[1,2] Adverse drug events caused by DDIs are preventable errors, which account for 2% to 3% of hospital admissions.[3] The prevalence of DDIs in hospitalized patients ranges from 15% to 45%.[1] Additionally, patients who are admitted to hospital because of DDIs often experience longer lengths of stay than patients admitted for other reasons.[4]

As medication specialists, pharmacists have a unique role on the interdisciplinary health care team, intervening on DDIs to prevent adverse drug events as part of their professional practice. Given the vast number of known DDIs, clinical decision support systems (CDSS) and computerized DDI checkers are used by pharmacists to help identify DDIs of clinical importance. However, CDSS have been shown to have suboptimal performance in the clinical management of DDIs.[2] For example, CDSS may be limited in their ability to detect updated and evidence-based clinically significant DDIs.[2] Moreover, the comprehensiveness of the databases used for the alerts can vary considerably.[2,5] Previous research has suggested that pharmacists perceive considerable discrepancies in the severity rankings of DDIs among various CDSS, which makes these systems difficult to view as reliable sources.[6,7] Additionally, when different pharmacists were given exactly the same CDSS-generated severity classification for various DDIs, there was poor agreement among the management strategies that they recommended.[6,7] These challenges can make it difficult for pharmacists to determine how to assess and properly manage DDIs encountered in practice.

Pharmacists are trained to develop and use a well-defined thought process to thoroughly manage DDIs as part of their provision of comprehensive patient care. A clinical thought process is a complex cognitive practice that involves clinical reasoning and critical problem-solving.[8,9] Pharmacy regulatory authorities in various countries have developed practice standards, which state that pharmacists are expected to critically analyze and apply information to make evidence-informed decisions within their practice.[10-12] The ability to competently fulfil these practice standards relies on the strength of a pharmacist's clinical thought process. Little is currently known or published about the challenges that newly qualified pharmacy practitioners encounter when managing DDIs in practice.[6,7,13]

Ultimately, the goal of developing a novel DDI management tool is to outline a clinical decision-making thought process to help pharmacists critically analyze and manage DDIs. The primary objective of our study was to develop a novel DDI management tool, and the secondary objective was to investigate practitioners' perceptions of this tool. The information from this study will provide insight into the clinical thought process that pharmacists utilize when assessing and managing DDIs in clinical practice.

METHODS

This study was conducted in 3 phases: development of the DDI management tool, implementation of the tool into clinical practice by study participants, and collection of participants' perceptions regarding the tool. The original study population included clinical and dispensary pharmacists working at 3 hospitals in British Columbia's Lower Mainland Pharmacy Services (LMPS) health authority (Vancouver General Hospital, St Paul's Hospital, and Surrey Memorial Hospital) and 28 LMPS hospital pharmacy residents training in the 2019/20 academic year. However, because of circumstances related to the COVID-19 pandemic, the study population for the third (survey) phase was amended to include only pharmacy residents. Pharmacists working at other hospitals, advanced pharmacy practice residents, pharmacy technicians or assistants, and community pharmacists were excluded from this study. Once developed, the DDI management tool was introduced and implemented at all study sites. Ethics approval for this study was granted by the University of British Columbia's Behavioural Research Ethics Board.

Phase 1: Development of the Tool

Development of the novel DDI management tool was accomplished through 4 distinct stages. Stage 1 focused on a comprehensive literature search to provide context for the DDI management tool. During stage 2, the study investigators created a preliminary version of the tool. Stage 3 involved analysis of the preliminary DDI management tool by an expert panel of pharmacist stakeholders. Stage 4 involved refinement of the tool and validation through simulations with sample DDIs.

Stage 1: Literature Search

A literature search was conducted to identify any previously published studies examining the development or evaluation of a DDI management tool for clinicians, as well as any studies examining clinical decision-making processes in the assessment of DDIs. Multiple databases were searched, specifically Ovid MEDLINE, Embase, PubMed, and Google Scholar, using the search terms "drug interaction", "algorithm" or "tool" or "initiative" or "software", "decision making" or "clinical decision" or "management" or "thought process", and "pharmacy" or "pharmacist" (with date limits from 1960 to 2020). Context for the tool was developed from the literature search and previous work by our study

group examining the perceptions and management of DDIs in hospital pharmacy over the course of several years.[6,7,14] The members of the study group had extensive expertise in advanced clinical pharmacy practice, having worked in hospital practice in various roles for over 10 years. Given the capacity of these team members and knowledge gained from previous research, the study group was well positioned to develop the DDI management tool.

Stage 2: Creation of a Preliminary Tool

The study investigators first developed a preliminary version of the tool by mirroring the various steps and clinical checkpoints that pharmacists complete when assessing a DDI. This process was outlined as an algorithm using workflow mapping techniques. Pertinent categories for DDI assessment were organized and a scoring system was developed on the basis of clinical relevance, at the study investigators' discretion. For this study, CDSS were defined as the clinical decision support systems or computerized DDI programs (e.g., Lexicomp, Wolters Kluwer Health; Micromedex, IBM) used by pharmacists when assessing DDIs to provide management suggestions.

Stage 3: Expert Evaluation of the Preliminary Tool

To minimize subjectivity and bias of the newly developed tool, an independent expert panel of key pharmacist stakeholders was invited to evaluate and provide feedback on the preliminary version. The panel consisted of content-matter experts and pharmacists with various levels of education who were practising in hospital settings. Each panelist independently reviewed the preliminary tool and provided feedback, which was then used by the study team to guide modifications for refining the tool.

Stage 4: Tool Finalization and Initial Testing

The final version of the tool underwent initial testing and validation through simulations using a list of 15 known DDIs previously evaluated by the study team and found to have differences between CDSS recommendations and pharmacists' actions in practice.[7] For each DDI, the management recommendations generated by the novel tool were compared with the data from pharmacists surveyed in our previous research.[7] On the basis of simulation results, additional revisions were considered, and the components of the tool were finalized through discussion with the study team.

Phase 2: Implementation of the Tool

Multiple modalities were used to disseminate the tool. An electronic PDF document of the tool and a video overview created by the investigators were sent by email to study participants through pharmacy administrative staff at each site. Paper handouts were also made available to the pharmacists. An infographic poster containing a QR code linked to a PDF version of the tool was posted in the pharmacies at each site to alert staff to the new tool. Additionally, in-person educational presentations were provided at the sites to further explain both the use of the tool and the study more generally. A total duration of 6 weeks was allowed for study participants to implement the TLC-Act tool in their practice before dissemination of the feedback survey.

Phase 3: Assessment of the Tool in Clinical Practice

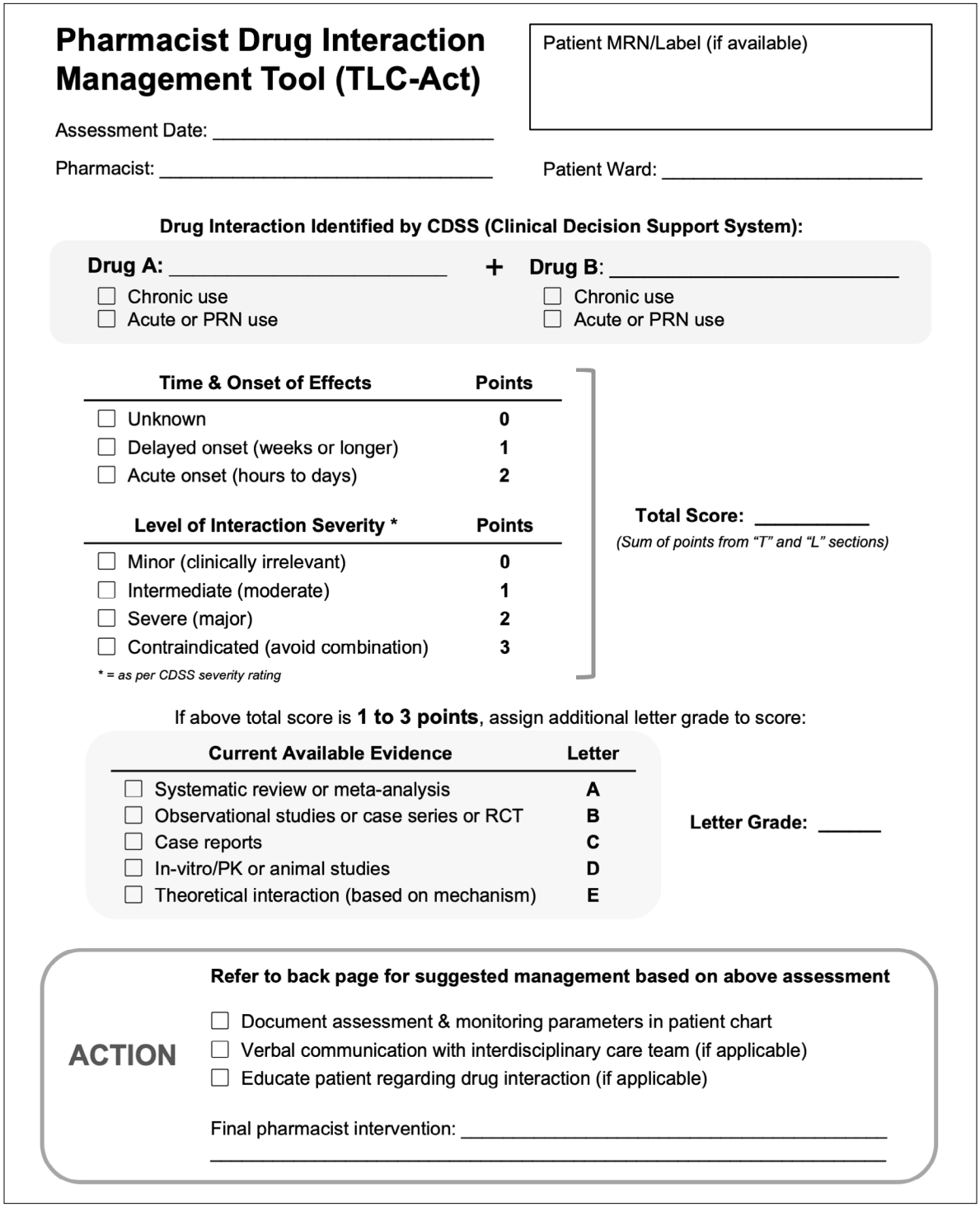
Feedback about the TLC-Act tool was solicited by means of a survey made available through the online platform Qualtrics (version February 2020). The residency program coordinator sent information about the survey to pharmacy residents by email, on behalf of the research team. Additionally, because the COVID-19 pandemic resulted in suspension of clinical rotations for the pharmacy residents during the 6-week implementation period, 2 additional paper-based practice cases were provided to survey participants to supplement their experience with use of the tool. The survey questions were developed by consensus among the investigators, and included questions pertaining to the organization and use of the tool. Informed consent to participate in the survey was implied by participation in the survey. The survey responses were collected through the Qualtrics platform (version February 2020) and analyzed with Excel spreadsheet software (version 16.41; Microsoft Corporation) using descriptive statistics.

RESULTS

Development and Final Components of the Novel DDI Management Tool (TLC-Act)

The novel DDI management tool was generated to map the clinical thought process of a pharmacist and to establish a systematic approach to managing DDIs. The tool incorporated a scoring system of components pertinent to assessing a DDI, as established by study investigators on the basis of their previous clinical experience. The literature search yielded no studies directly relevant to our search criteria, and no DDI management strategies or tools were identified. Therefore, the final components of the TLC-Act tool were decided upon through discussion by the study team, evaluation of the tool by the expert panel, and simulated use against a list of DDIs known from our previous research. A total of 9 hospital pharmacists with various roles at different sites constituted the expert panel, which independently evaluated the tool and provided recommendations for revision. The tool underwent a total of 8 revisions during the development phase, with each revision being completed through review and discussion among members of the study team. There was a high level of agreement between the DDI management strategies recommended by the TLC-Act tool and the preferred actions taken by pharmacists in clinical practice, as determined in a previous survey study regarding DDI management (with matching for 14 of 15 recommendations).[7]

The 3 main sections of the tool used for scoring a DDI referred to the time frame for onset of effects from the DDI, the severity rating generated by the CDSS, and the level of available evidence for the interaction. Information related to time of onset of effects and level of interaction severity (i.e., the T and L sections of the tool), generated a combined total score that was then used to determine the suggested strategy for managing the DDI (Figure 1A). If the total



Pharmacist Drug Interaction Management Tool (TLC-Act)

Patient MRN/Label (if available)

Assessment Date: _____

Pharmacist: _____ Patient Ward: _____

Drug Interaction Identified by CDSS (Clinical Decision Support System):

Drug A: _____ + **Drug B:** _____

☐ Chronic use ☐ Acute or PRN use ☐ Chronic use ☐ Acute or PRN use

Time & Onset of Effects	Points
☐ Unknown	0
☐ Delayed onset (weeks or longer)	1
☐ Acute onset (hours to days)	2

Level of Interaction Severity *	Points
☐ Minor (clinically irrelevant)	0
☐ Intermediate (moderate)	1
☐ Severe (major)	2
☐ Contraindicated (avoid combination)	3

* = as per CDSS severity rating

Total Score: _____
(Sum of points from "T" and "L" sections)

If above total score is **1 to 3 points**, assign additional letter grade to score:

Current Available Evidence	Letter
☐ Systematic review or meta-analysis	A
☐ Observational studies or case series or RCT	B
☐ Case reports	C
☐ In-vitro/PK or animal studies	D
☐ Theoretical interaction (based on mechanism)	E

Letter Grade: _____

ACTION

Refer to back page for suggested management based on above assessment

☐ Document assessment & monitoring parameters in patient chart
☐ Verbal communication with interdisciplinary care team (if applicable)
☐ Educate patient regarding drug interaction (if applicable)

Final pharmacist intervention: _____
_____

FIGURE 1A. TLC-Act, a novel tool for management of drug–drug interactions (DDIs), outlining a pharmacist's clinical thought process for assessing a DDI (part 1 of 2). Components of the tool include time and onset of effects from the DDI, severity of the interaction, and currently available evidence for the DDI. For each DDI, the tool yields a total score and letter grade that are then used to generate a management strategy (second page of the tool: see Figure 1B). PK = pharmacokinetic, PRN = as needed, RCT = randomized controlled trial. © 2019 Lower Mainland Pharmacy Services, British Columbia. Reproduced by permission.

score was between 1 and 3 points, the user was instructed to complete the section for "current available evidence" (i.e., the C section of the tool shown in Figure 1A). This section was based on available evidence (summarized from the CDSS or obtained through a literature search performed by the pharmacist) and generated a letter grade.

Using both the combined total score (from the T and L sections) and, if applicable, the letter grade (from the C section), the tool then suggested a management strategy for the DDI (i.e., the "Act" section of the tool). For this section of the tool, the user had to complete documentation for actions or interventions undertaken to manage the DDI, including communication with the patient's care team and education provided to the patient (Figure 1A). Suggested management recommendations determined from the total score and letter grade were provided on the second page of the tool (Figure 1B). Based on the user's consideration of additional case-specific factors, including the frequency of administration for the interacting medications and the presence of other patient-specific factors that could increase the risk of an adverse effect from the DDI, the tool generated recommendations for management approaches. Examples of other patient-specific risk factors might include renal or liver dysfunction, critical illness, or high medication dosages. Evaluation of a patient's risk factors was based on the practitioner's clinical judgment, which was not limited by the tool. According to the information used to assess the interaction, the TLC-Act tool recommended one of the following management approaches: monitoring (no change in drug therapy required), consideration of an intervention and drug therapy change, or recommendation for an intervention and drug therapy change (Figure 1B).

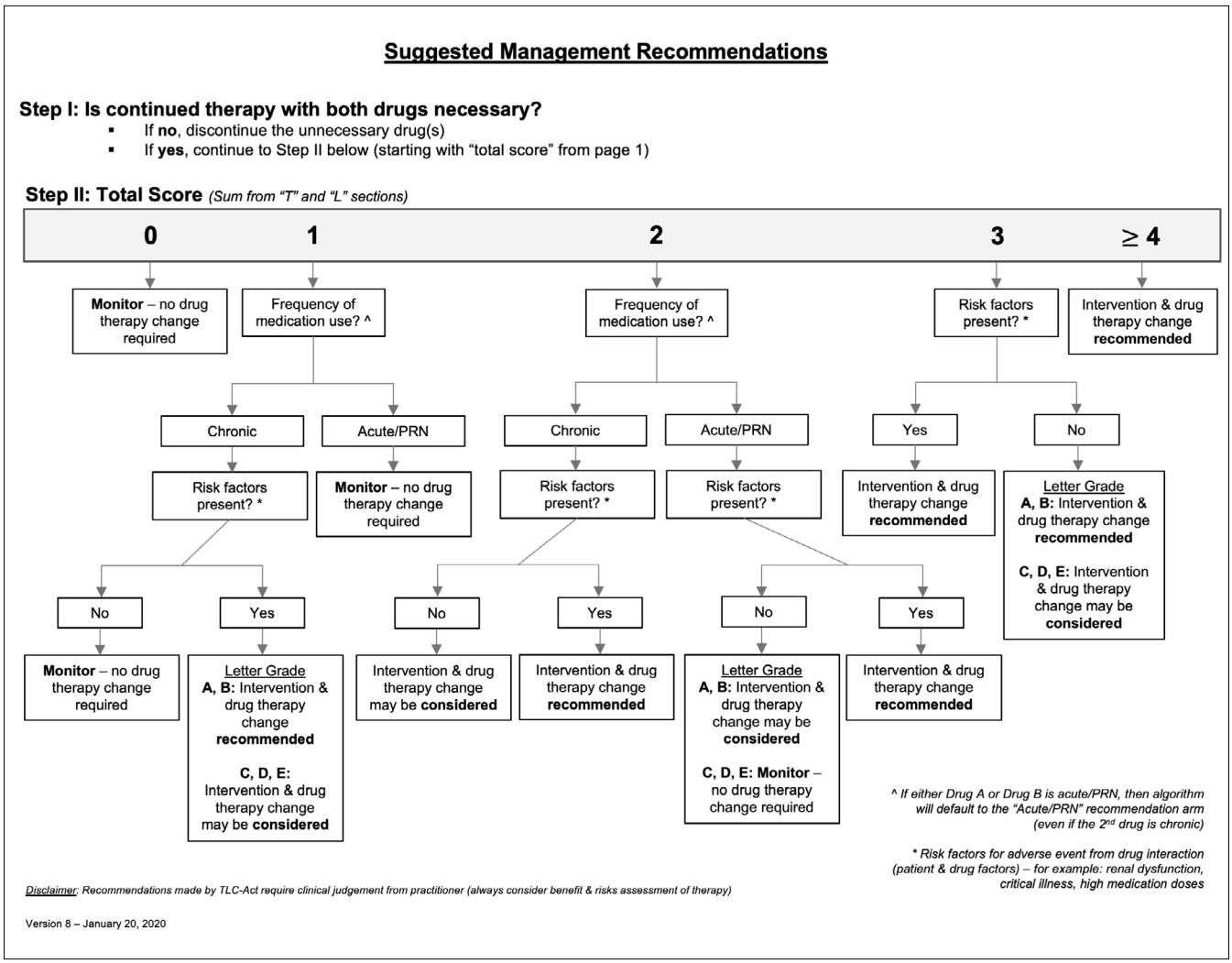


FIGURE 1B. TLC-Act, a novel tool for management of drug–drug interactions (DDIs), outlining a pharmacist's clinical thought process for assessing a DDI (part 2 of 2). For each DDI, the tool yields a total score and letter grade (as shown in Figure 1A), which are then used to generate a suggested management strategy. Additional components, specifically the frequency of drug administration and the presence of patient-specific risk factors, are considered to determine the suggested management strategy. PRN = as needed. © 2019 Lower Mainland Pharmacy Services, British Columbia. Reproduced by permission.

Implementation of the Tool

The novel DDI management tool was introduced and implemented at all 3 study sites in February 2020, with a target study population of more than 500 hospital pharmacists. However, because of circumstances surrounding the COVID-19 pandemic, many pharmacists working at the 3 target sites were unable to participate in our assessment survey. We were unable to quantify the total number of pharmacists who used the tool in clinical practice during our study or the duration of use. Pharmacy residents had an average of 4 weeks to implement the tool, which was shortened from the planned implementation period of 6 weeks when clinical rotations were suspended as a result of the COVID-19 pandemic.

Assessment of the Tool in Clinical Practice

Although both pharmacists and pharmacy residents had an opportunity to implement the TLC-Act tool in their clinical practice, assessment of the tool focused solely on the perspectives of pharmacy residents, for the reasons outlined above. The assessment survey consisted of 13 Likert-style questions to reflect the usability, feasibility, and utility of the tool (Supplement 1, available from https://www.cjhp-online.ca/index.php/cjhp/issue/view/209). Of the 28 pharmacy residents who participated in implementing the novel DDI management tool, 15 provided feedback (response rate 54%).

Overall, the TLC-Act tool was rated by survey respondents as slightly more useful than usual care, where usual care was defined as the use of CDSS or DDI computerized software (e.g., Lexicomp, Micromedex) alone for managing a DDI (Figure 2). When asked to rate the usability of the tool, 13 (87%) of the survey respondents found that the tool had logical flow, and 9 (60%) found it easy to use. In addition, the majority of respondents felt that the amounts of time and information required to use the tool were appropriate. On average, the time required to assess a

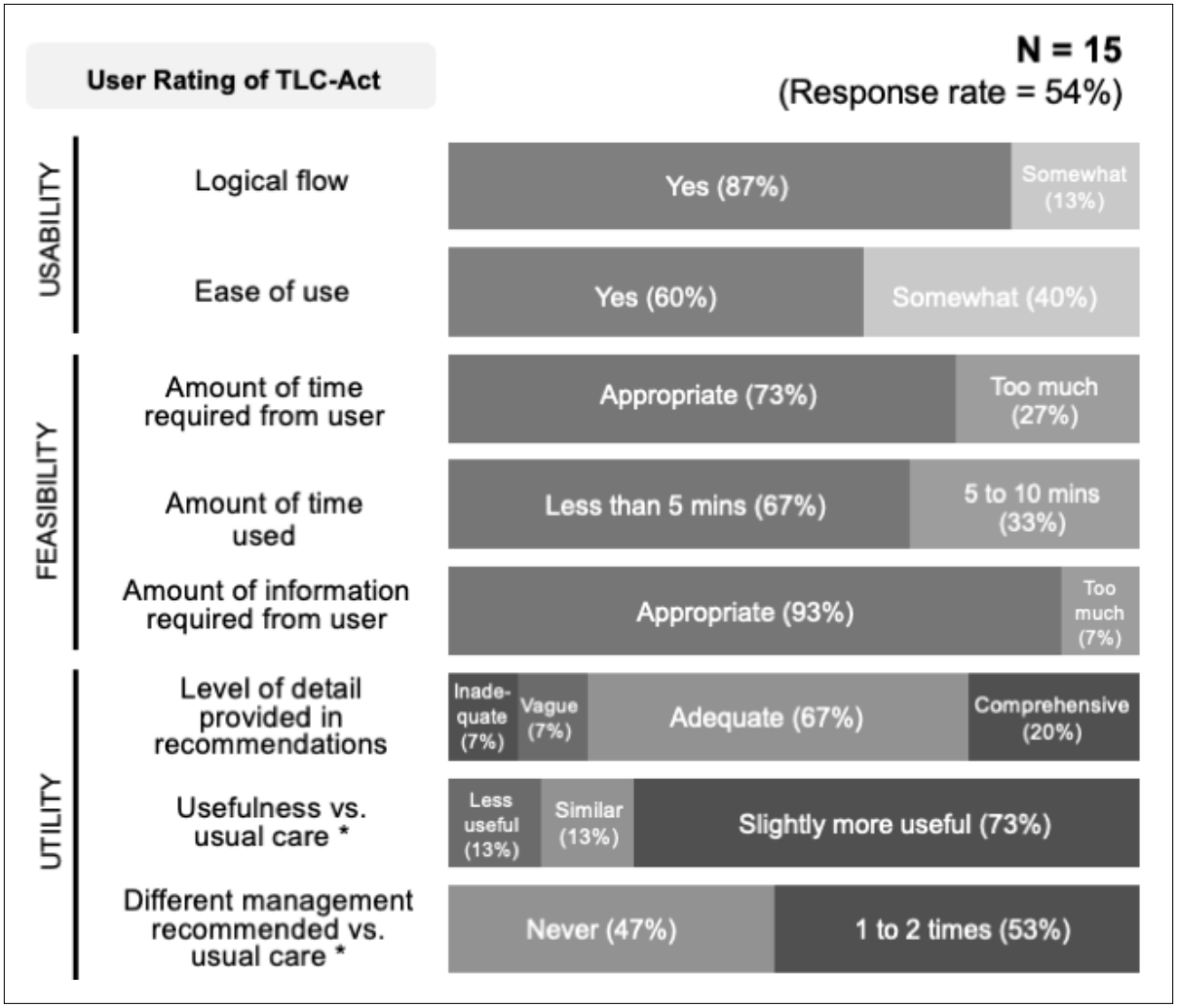


FIGURE 2. Results of the online feedback survey evaluating TLC-Act, the novel tool for management of drug–drug interactions (DDIs). The survey was organized to assess the usability, feasibility, and utility of the tool. The survey response rate was 54% (15/28). The figure displays only survey options that were selected by respondents. *Usual care was defined as use of a clinical decision support system or DDI software (e.g., Lexicomp, Micromedex) alone, without reference to the TLC-Act tool.

single DDI with the TLC-Act tool was less than 5 minutes for two-thirds of survey respondents. When asked to rate the utility of the tool for practice, two-thirds of respondents believed that the level of detail provided by the recommendations was adequate.

All of the pharmacy residents who responded to the feedback survey reported that they would consider recommending the tool to other pharmacists for assessing DDIs. However, only 5 (33%) said they would consider recommending the tool to other pharmacists in its current form, without further revisions. Suggested revisions for the tool (which were provided as free text) included reducing the time to use the tool and minimizing the need for manual calculations. Additionally, 9 (60%) respondents were not using the tool in clinical practice when they responded to the survey. Instead, these participants evaluated the TLC-Act tool using the 2 practice clinical cases provided to the residency class. The other 6 (40%) respondents had each used the TLC-Act tool in clinical practice from 1 to 3 times during the implementation phase.

DISCUSSION

The findings of this study suggest that use of the TLC-Act tool, in combination with already-established CDSS, may support clinical decision-making by hospital pharmacy residents when they are assessing DDIs. Previous research has suggested inconsistencies between how DDIs are categorized by CDSS and how pharmacists use the information supplied by CDSS in clinical practice, which raises questions about the utility of these computerized systems.[6,7]

Although the interacting medications themselves have substantial effects on the severity of DDIs and the urgency of acting upon them, many other factors influence how an interaction should be managed. Our novel algorithm sought to incorporate these additional factors to better guide clinicians in their decision-making processes. How an interaction is managed is largely influenced by factors specific to the patient who is taking the interacting medications, for example, risk factors that might increase the probability of experiencing an adverse effect or the frequency of administration of the medications. Furthermore, clinicians may consider the level of evidence available about the specific DDI. Because of the relatively low incidence of DDIs reported in the literature, clinicians must critically evaluate whether the available evidence is applicable to the specific patient or the interacting medications being assessed. For example, the interaction between escitalopram and enoxaparin is considered a moderate-severity DDI, and computerized interaction systems typically recommend that the clinician consider modifying the patient's drug therapy according to the manufacturers' prescribing information related to increased bleeding complications with medications that have antiplatelet properties.[15] However, no specific evidence pertaining directly to the interaction between escitalopram and enoxaparin is available in the literature. Therefore, for patients receiving prophylactic doses of enoxaparin for prevention of venous thromboembolism (VTE) during an acute care inpatient admission, it may be more appropriate to monitor for bleeding complications than to alter the patient's long-term antidepressant therapy. Overall, because recommendations generated by CDSS are generic in nature and do not account for patient- or case-specific factors (e.g., medication dosages, clinical context, or duration of therapy), such management strategies may be more conservative than necessary.

With those considerations in mind, our research team developed the TLC-Act tool to provide an alternative approach to managing DDIs. Returning to the example of escitalopram and enoxaparin, the TLC-Act tool categorizes the interaction as "1E" (i.e., unknown reaction onset, CDSS rating of moderate severity, and theoretical interaction based on mechanism), for which the recommendation is to monitor for an adverse drug event (i.e., no change in drug therapy required) if the patient is using the concomitant medications for an acute indication such as VTE prophylaxis during an inpatient admission. Conversely, if the patient is expected to use both medications for chronic indications (e.g., VTE treatment) and patient-specific factors are present that could increase the possibility of an adverse effect (i.e., bleeding complication), an intervention and drug therapy change may be considered. As such, the recommendations provided by the TLC-Act tool may represent a more realistic management approach for practice than traditional CDSS recommendations.

Preliminary assessment of the TLC-Act tool based on feedback gathered by surveying hospital pharmacy residents suggested a reasonable degree of usability and utility. Limitations of the current version of the tool include the constraint of testing one DDI at a time and the need for manual calculations. Improvements might be aimed at transitioning to an electronic application, to allow for automatic calculations and assessment of multiple interacting medications, thus improving usability. Another limitation was the small cohort of pharmacy residents who participated in the evaluation survey, given that the original study population of pharmacists had to be excluded from the survey because of workload constraints related to the COVID-19 pandemic. As a result, use of TLC-Act as a clinical tool requires validation with a larger population of pharmacists. The TLC-Act tool primarily functions as a step-by-step method for assessing a DDI; it may have less utility for experienced clinicians for whom these steps have become more automatic. However, based on implementation of the TLC-Act tool in this study and the information gathered, there may be value in using the tool as a teaching aid to support new clinicians, such as pharmacy residents or students, as they develop clinical decision-making skills pertaining to DDI management.

CONCLUSION

The TLC-Act is a novel DDI management tool designed for pharmacists and new clinicians, which may support development of a clinician's clinical thought process and a systematic approach to assessing DDIs. Survey responses from hospital pharmacy residents provide a preliminary understanding of the usability and utility of the TLC-Act tool. Most survey respondents perceived the TLC-Act tool to be slightly more useful than usual care for managing DDIs. Because pharmacy residents and students are learning to build their clinical decision-making skills, the TLC-Act tool may have value as a teaching aid to support development of a systematic thought process.

Future directions include implementing the TLC-Act tool into an entry-to-practice Doctor of Pharmacy program curriculum to allow exploration of its utility as a clinical decision teaching aid for pharmacy students. By training pharmacy learners and new pharmacists to use these steps in their clinical reasoning and thought process, our study team hopes the tool will lead to eventual improvements in clinical outcomes for patients by minimizing adverse effects from DDIs.

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Exploration de l'association possible entre la consommation d'antibiotiques et l'émergence de résistance dans un centre hospitalier universitaire mère-enfant

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RÉSUMÉ

Contexte : L'émergence de résistances aux antibiotiques a contribué à créer des bactéries multirésistantes, et ceci constitue une préoccupation majeure.

Objectifs : L'objectif principal était d'explorer l'association possible entre la consommation d'antibiotiques et l'émergence de résistance dans un centre hospitalier universitaire mère-enfant.

Méthode : Il s'agit d'une étude rétrospective menée dans un centre hospitalier universitaire. Des couples antibiotique-bactérie ont été établis, en tenant compte du nombre d'isolats, de l'utilisation réelle d'antibiotique et de la pertinence clinique des couples. Pour chaque couple, une comparaison de deux variables (consommation d'antibiotiques et pourcentage de résistance) a été quantifiée par un coefficient de Pearson. Trois analyses ont été considérées : sans décalage entre les données d'utilisation et de résistance, décalage d'un an et décalage de deux ans.

Résultats : Trente couples ont été sélectionnés en hémato-oncologie et 18 couples en néonatologie. En hémato-oncologie, six couples avaient une corrélation positive (Pearson > 0,7), deux couples impliquant le méropénem, deux la ceftazidime et deux la pipéracilline-tazobactam. Dans trois cas, la corrélation s'observe sans décalage entre les données de consommation et de résistance. En néonatologie, trois couples avaient une corrélation positive, un impliquant la vancomycine, un la cloxacilline et un le méropénem.

Conclusions : Il est possible d'explorer l'association qui peut exister entre la consommation d'antibiotiques et l'émergence de résistance dans un centre. L'approche exploratoire reposait sur un traitement manuel des données. Il pourrait être intéressant d'envisager une approche systématique continue permettant la production automatique de corrélations.

Mots-clés : antimicrobiens, résistance, bon usage, antibiogouvernance

ABSTRACT

Background: The emergence of antibiotic resistance has contributed to the development of multidrug-resistant bacteria, which is a major concern.

Objectives: The primary objective was to explore the possible association between antibiotic use and the emergence of resistance in a mother-child university hospital.

Method: This retrospective study was conducted in a university hospital centre. Antibiotic-bacteria pairs were established, taking into account the number of isolates, actual antibiotic use, and clinical relevance. For each pair, a comparison of 2 variables (antibiotic utilization and rate of resistance) was quantified with the Pearson coefficient. Three analyses were conducted: no lag between utilization and resistance, 1-year lag, and 2-year lag.

Results: Thirty antibiotic-bacteria pairs were selected from hematology-oncology and 18 from neonatology. In hematology-oncology, 6 pairs had a positive correlation (Pearson coefficient > 0.7): 2 pairs involving meropenem, 2 involving ceftazidime, and 2 involving piperacillin-tazobactam. In 3 of these cases, there was no lag between consumption of antibiotics and presence of resistance. In neonatology, 3 antibiotic-bacteria pairs had a positive correlation, 1 each involving vancomycin, cloxacillin, and meropenem.

Conclusions: It is possible to explore the potential association between consumption of antibiotics and emergence of resistance in a particular centre. Our exploratory approach was based on manual data processing. It would be interesting to consider a continuous systematic approach, allowing automatic generation of correlations.

Keywords: antimicrobials, resistance, appropriate use, antibiotic management

INTRODUCTION

La découverte des antibiotiques et leur utilisation en médecine remontent à moins d'un siècle et constituent une avancée importante de la médecine. Dès les premières années d'utilisation, l'apparition de résistances aux antibiotiques et l'émergence de bactéries multirésistantes ont été observées[1,2]. Ces bactéries constituent un problème de santé publique, car elles deviennent difficiles à traiter et contribuent à des échecs thérapeutiques associés à la morbidité

et à la mortalité. Strathdee *et al.* rapportent que l'antibiorésistance est associée à plus de 700 000 morts par an dans le monde et qu'elle serait associée à la mort d'environ 10 millions de personnes par an d'ici 2050, ce qui coûtera 100 000 milliards de dollars à l'économie mondiale en raison d'une perte de productivité[3]. Au Canada, plusieurs organismes surveillent l'émergence de résistance, tels que le Canadian Antimicrobial Resistance Surveillance System[4] et le Programme canadien de Surveillance des infections nosocomiales[5] de l'Agence de la santé publique du Canada ou l'initiative Canadian Antimicrobial Resistance Alliance[6].

L'Organisation mondiale de la santé (OMS) a fait de la prévention et la gestion de la résistance aux antibiotiques une priorité stratégique en 2015[7]. Le plan proposé comporte cinq objectifs, soit « d'améliorer la sensibilisation et la compréhension de la résistance aux antimicrobiens, de renforcer la surveillance et la recherche pour réduire l'incidence des infections, de réduire l'incidence des infections, d'optimiser l'utilisation des médicaments antimicrobiens et d'assurer un investissement durable dans la lutte contre la résistance aux antimicrobiens »[7].

Du fait de leur résistance à certains antibiotiques et du nombre important d'infections, sept bactéries sont sous l'attention particulière de l'OMS. Parmi ces bactéries, trois sont à l'origine d'infections en milieu hospitalier : *Escherichia coli* résistant aux céphalosporines de 3^{e} génération et aux fluoroquinolones, *Klebsiella pneumoniae* résistant aux céphalosporines de 3^{e} génération et aux carbapénèmes et *Staphylococcus aureus* résistant à la méticilline[8]. Le plan d'action mondial pour combattre la résistance aux antimicrobiens prévoit que chaque état membre doit fournir des programmes de bonne gestion afin de contrôler et d'optimiser l'emploi des anti-infectieux au niveau national[9].

Dans la même optique, l'OMS a aussi développé la classification AWaRe pour l'ensemble des antibiotiques. Le classement des antibiotiques propose trois groupes pour optimiser leur utilisation : le groupe « Access » comprend 48 antibiotiques ne comportant pas d'enjeu de résistance pour le moment, le groupe « Watch » compte 110 antibiotiques à haut risque de résistances et le groupe « Reserve » comporte 22 antibiotiques dont l'usage doit être limité et contrôlé[10].

Au Canada, une pratique organisationnelle exigeant une gérance des antimicrobiens a contribué à la collecte et à l'analyse de données de consommation des antibiotiques dans le cadre des activités d'antibiogouvernance menées dans chaque établissement de santé[11]. Au Québec, le comité sur les infections nosocomiales du Québec (CINQ) a publié un rapport sur les infections nosocomiales et l'intérêt d'assurer une surveillance de l'utilisation des antimicrobiens[12]. Dans la foulée de ce rapport, le ministère de la Santé et des Services sociaux a publié en 2011 une circulaire administrative afin d'assurer la mise en œuvre d'un programme de surveillance de l'usage des antibiotiques en établissement de santé[13]. De plus, le CINQ a mis en place un Comité central de surveillance provinciale des infections nosocomiales[14]. En réponse à cette circulaire administrative, chaque établissement de santé du Québec collige annuellement des données de consommation de ses antimicrobiens. Au Québec, Delisle *et al.* ont publié le profil de leur antibiogramme cumulatif[15].

Afin de profiter des données colligées périodiquement, nous nous sommes intéressés à l'utilisation des antimicrobiens et à l'émergence de résistance à ces médicaments au sein de notre établissement. Nous proposons une méthodologie génératrice d'hypothèse pour alimenter les travaux d'équipes en antibiogouvernance.

MÉTHODE

Il s'agit d'une étude rétrospective et descriptive. L'objectif principal était d'explorer l'association possible entre la consommation d'antibiotiques et l'émergence de résistance dans un centre hospitalier universitaire mère-enfant.

Population à l'étude

L'étude se déroule dans un centre hospitalier universitaire mère-enfant de 500 lits. Deux clientèles ont été ciblées, soit l'hémato-oncologie et la néonatologie, comme il s'agit de sous-populations homogènes dans notre établissement en termes de caractéristiques de patients et d'habitudes d'utilisation d'antibiotiques par les prescripteurs. L'étude porte sur les données de consommation de 2005-2006 à 2017-2018 et les données de résistance de 2007-2008 à 2017-2018. Ce recul additionnel de deux ans de consommation a été retenu de façon arbitraire, en présumant un délai minimal nécessaire à la détection de la résistance.

Bactéries et résistance

Les données de résistance reposant sur un minimum de 30 isolats en moyenne par année et par unité de soins ont été considérées. Un nombre insuffisant d'isolats pouvait être corrigé par le regroupement d'années ou d'espèces semblables (les données détaillées sont disponibles sur demande auprès de l'auteur correspondant). Les données recueillies provenaient de l'antibiogramme cumulatif institutionnel. L'antibiogramme est produit selon les balises du Clinical and Laboratory Standards Institute[16]. Une valeur de sensibilité intermédiaire a été recodée comme résistante.

Consommation d'antibiotiques

En pédiatrie, la consommation d'antibiotiques est mieux décrite par jours de traitement que par dose définie journalière[17,18]. Ainsi, le nombre de jours de traitements (JT) a été extrait pour chaque antibiotique et pour chaque unité d'hospitalisation à partir du dossier pharmacologique informatisé (GesphaRx, CGSI TI). Par la suite, le nombre de jours de traitement pour 1000 jours-présences (JT/1000JP) a été calculé pour chaque antibiotique par unité d'hospitalisation. Les données de consommation reposant sur un minimum de

10 JT/1000JP en moyenne par année ont été considérées (seuil décidé arbitrairement). Les antibiotiques sélectionnés étaient: amikacine, amoxicilline-acide clavulanique, ampicilline, céfazoline, céfixime, ceftazidime, ceftriaxone, ciprofloxacine, clindamycine, cloxacilline, erythromycine, gentamicine, lévofloxacine, linézolide, méropénem, nitrofurantoïne, pipéracilline-tazobactam, rifampicine, tobramycine, triméthoprime-sulfaméthoxazole (TMP-SMX) et vancomycine.

Plan d'analyse

Afin d'explorer l'association possible entre la consommation d'antibiotiques et l'émergence de résistance, des couples antibiotique-bactérie ont été établis, en tenant compte du nombre d'isolats (minimum de 30 isolats en moyenne par année), de l'utilisation réelle d'antibiotique (au moins 10 JT/1000JP en moyenne) et de la pertinence clinique des couples.

Pour chaque couple identifié, une comparaison des deux variables (consommation d'antibiotiques (JT) et pourcentage de résistance) a été quantifiée par le calcul d'un coefficient de Pearson. Trois points de vue ont été considérés : analyse sans décalage (c.-à-d. les données d'utilisation et de résistance proviennent de la même année), analyse avec décalage d'un an (c.-à-d. les données d'utilisation précèdent d'une année les données de résistance) et analyse avec décalage de deux ans entre la consommation et les résistances observées. De façon arbitraire, les données illustrant une corrélation supérieure à 0,7 ont été illustrées. Seules des statistiques descriptives ont été effectuées.

RÉSULTATS

Bactéries

En hémato-oncologie pédiatrique, 2653 requêtes d'antibiogramme ont été réalisées pour 1319 dossiers de patients entre 2007-2008 et 2017-2018. Les bactéries *Escherichia coli*, *Staphylococcus aureus* et *Staphylococcus epidermidis* présentaient un nombre suffisant d'isolats. En raison de leur nombre insuffisant d'isolats par année, les bactéries *Enterobacter* spp, *Citrobacter* spp, *Morganella* spp et *Serratia* spp ont été regroupées pour former le groupe des Entérobactéries. Pour ce qui est de *Klebsiella* spp, *Enterococcus* spp, *Pseudomonas* spp, Staphylocoques coagulase négative (SCN), le nombre insuffisant d'isolats par année a été corrigé par le regroupement de 2 années successives. Les autres bactéries n'ayant pas atteint le nombre moyen de 30 isolats par année ont été exclues.

En néonatologie, 2653 requêtes d'antibiogramme ont été réalisées pour 1535 dossiers de patients entre les années 2007-2008 et 2017-2018. Les bactéries *Enterococcus* spp. *Escherichia coli*, *Klebsiella* spp et trois espèces de *Staphylococcus* (*S. aureus*, *S. epidermidis*, SCN) présentaient un nombre suffisant d'isolats. En raison de leur nombre insuffisant d'isolats par année, les bactéries *Enterobacter* spp, *Citrobacter* spp, *Morganella* spp et *Serratia* spp ont été regroupées pour former le groupe Entérobactéries. En raison du nombre toujours insuffisant d'isolats, les autres bactéries n'ont pas été retenues pour l'étude.

Consommation d'antibiotiques

La description de la consommation d'antibiotiques en JT/1000JP pour le service d'hémato-oncologie est disponible sur demande auprès de l'auteur correspondant. Les antibiotiques sélectionnés pour l'étude dans le service d'hémato-oncologie étaient les suivantes : ceftazidime, ceftriaxone, ciprofloxacine, cloxacilline, lévofloxacine, méropénem, pipéracilline-tazobactam, tobramycine, TMP-SMX et vancomycine. Les autres n'atteignaient pas la consommation moyenne de 10 JT/1000JP et ont été exclus.

La description de la consommation d'antibiotiques en JT/1000JP pour le service de néonatologie est disponible sur demande auprès de l'auteur correspondant. Les antibiotiques sélectionnés pour l'étude dans le service de néonatologie étaient les suivantes : ampicilline, cloxacilline, gentamicine, linézolide, méropénem, pipéracilline-tazobactam et vancomycine. Les autres n'atteignaient pas la consommation moyenne de 10 JT/1000JP et ont été exclus.

Couples bactérie-antibiotique choisis pour l'étude

Après la sélection des bactéries et des antibiotiques, des couples bactérie-antibiotique ont été sélectionnés en fonction de la pertinence clinique. Trente couples ont été sélectionnés en hémato-oncologie (tableau 1) et dix-huit couples en néonatologie (tableau 2). Les données d'évolution des pourcentages de résistance aux antibiotiques pour ces couples respectifs sont disponibles sur demande auprès de l'auteur correspondant.

Étude de la corrélation entre l'évolution de la consommation d'antibiotiques et l'évolution des résistances aux antibiotiques

L'analyse de chaque couple sélectionné en hémato-oncologie est présentée (tableau 3). Les couples présentant une corrélation positive (valeurs entre 0,7 et 1) sans décalage d'années entre la consommation des antibiotiques (JT) et les résistances sont *Klebsiella* spp-méropénem (0,92), *Pseudomonas* spp-pipéracilline-tazobactam (0,84) et entérobactéries-ceftazidime (0,81). Les couples présentant une corrélation positive avec décalage de deux ans entre la consommation des antibiotiques et les résistances sont *Pseudomonas* spp-ceftazidime (0,93), entérobactéries-méropénem (0,82) et *Klebsiella* spp-pipéracilline-tazobactam (0,77) (tableau 3, figure 1).

L'analyse de chaque couple sélectionné en néonatologie est présentée (tableau 4). Les couples présentant une corrélation positive (valeurs entre 0,7 et 1) sans décalage d'années entre la consommation des antibiotiques (JT) et les résistances sont *Staphylococcus epidermidis*-vancomycine (0,85) et entérobactéries-méropénem (0,71). Le couple présentant

une corrélation positive avec décalage d'une année entre la consommation des antibiotiques et les résistances est *Staphylococcus aureus*-oxacilline (0,76) (tableau 4, figure 2).

DISCUSSION

Grammatico-Guillon et collab. ont évalué l'effet d'un programme d'antibiogouvernance en pédiatrie (c.-à-d. programme multidisciplinaire qui met à contribution l'expertise de médecins, pharmaciens et autres professionnels pour assurer le bon usage des antimicrobiens)[19]. Un index a également été créé pour considérer le spectre des antibiotiques en plus du volume d'utilisation; il facilite également les comparaisons entre hôpitaux[20]. Des 16 programmes inclus dans la revue narrative, un seul a contribué à la réduction des résistances aux antibiotiques.

Ainsi, Horikoshi et collab. ont noté une corrélation positive entre le taux de résistance aux carbapénèmes chez *Pseudomonas aeruginosa* et le nombre de JT (0,76, $p = 0,04$)[21]. Le taux de résistance ($p < 0,01$) et le nombre de JT ($p < 0,01$) ont diminué de manière significative dans la période post-intervention visant un usage optimal. Les auteurs de cette revue narrative notent que bien que l'antibiogouvernance soit une pratique exemplaire, il existe très peu de données sur les retombées de ce type de programme sur l'antibiorésistance[21].

Bell et collab. ont effectué une revue systématique afin d'explorer le lien entre l'utilisation d'antimicrobiens et la prévalence de résistance à ces agents[22]. Des 243 études retenues, les auteurs notent une relation positive et statistiquement significative entre la consommation d'antimicrobiens et la résistance, mais la modélisation par régression multiple n'a pas permis d'identifier des variables prédictrices. Les auteurs notent que ce lien d'association est plus fort dans les pays du sud de l'Europe. Costelloe et collab. ont également noté un lien entre l'utilisation et la résistance[23].

TABLEAU 1. Couples sélectionnés en hémato-oncologie

Bactéries	Ceftazidime	Ciprofloxacine	Méropénem	Oxacilline[a]	Pipéracilline-tazobactam	Tobramycine	TMP /SMX	Vancomycine
Entérobactéries	X	X	X		X	X		
Entrococcus spp								X
Escherichia coli	X	X	X		X	X		
Klebsiella spp	X	X	X		X	X		
Pseudomonas spp	X	X	X		X	X		
Staphylococcus aureus				X			X	X
SCN				X			X	X
Staphylococcus epidermidis				X			X	X

SCN = staphylocoques coagulase négative; TMP/SMX = triméthoprime-sulfaméthoxazole.
[a] L'analyse de la résistance est effectuée pour l'oxacilline et cible l'utilisation de cloxacilline.

TABLEAU 2. Couples sélectionnés en néonatologie

Bactéries	Ampicilline	Gentamicine	Méropénem	Oxacilline[a]	Pipéracilline-tazobactam	Vancomycine
Entérobactéries		X	X		X	
Entrococcus spp	X					X
Escherichia coli	X	X	X		X	
Klebsiella spp		X	X		X	
Staphylococcus aureus				X		X
SCN				X		X
Staphylococcus epidermidis				X		X

SCN = staphylocoques coagulase négative.
[a] L'analyse de la résistance est effectuée pour l'oxacilline et cible l'utilisation de cloxacilline.

Shapiro et collab. ont mis en évidence que la forte consommation d'antibiotiques a une plus forte influence sur l'incidence des infections par les pathogènes les plus résistants[24].

Dans notre étude, nous observons une corrélation positive (c.-à-d. supérieure à un coefficient de Pearson de 0,7) pour six couples antibiotique-bactérie en hémato-oncologie, soit deux couples impliquant le méropénem, deux pour la ceftazidime et deux pour la pipéracilline-tazobactam. Dans trois cas, la corrélation s'observe sans décalage entre les données de consommation et les données de résistance

TABLEAU 3. Corrélation entre l'évolution de la consommation d'antibiotiques et l'évolution des résistances aux antibiotiques pour le service d'hémato-oncologie

Bactéries	Antibiotiques	Pearson sans décalage	Pearson décalé 1 an	Pearson décalé 2 ans
E. coli	Ceftazidime	0,120	0,014	–0,239
E. coli	Ciprofloxacine	0,005	0,308	–0,405
E. coli	Méropénem	NA	NA	NA
E. coli	Pipéracilline-tazobactam	–0,073	–0,229	–0,238
E. coli	Tobramycine	–0,135	–0,247	–0,182
S. aureus	Oxacilline	0,257	0,683	0,491
S. aureus	TMP/SMX	–0,580	–0,293	–0,310
S. aureus	Vancomycine	–0,104	0,117	0,616
S. epidermidis	Oxacilline	–0,097	–0,110	–0,125
S. epidermidis	TMP/SMX	–0,228	–0,271	–0,511
S. epidermidis	Vancomycine	–0,222	–0,185	–0,246
SCN	Oxacilline	–0,819	NA	–0,132
SCN	TMP/SMX	–0,253	NA	–0,955[b]
SCN	Vancomycine	–0,473	NA	–0,703[b]
Klebsiella spp	Ceftazidime	–0,039	NA	–0,610
Klebsiella spp	Ciprofloxacine	–0,344	NA	–0,159
Klebsiella spp	Méropénem	0,917[a]	NA	0,207
Klebsiella spp	Pipéracilline-tazobactam	0,520	NA	0,768[a]
Klebsiella spp	Tobramycine	–0,474	NA	–0,775[b]
Enterobactéries	Ceftazidime	0,807[a]	NA	0,649
Enterobactéries	Ciprofloxacine	–0,350	NA	0,340
Enterobactéries	Méropénem	–0,572	NA	0,824[a]
Enterobactéries	Pipéracilline-tazobactam	–0,259	NA	–0,491
Enterobactéries	Tobramycine	–0,955[b]	NA	–0,777[b]
Enterococcus spp	Vancomycine	0,084	NA	–0,635
Pseudomonas spp	Ceftazidime	0,287	NA	0,933[a]
Pseudomonas spp	Ciprofloxacine	0,250	NA	0,004
Pseudomonas spp	Méropénem	0,249	NA	0,689
Pseudomonas spp	Pipéracilline-tazobactam	0,841[a]	NA	0,669
Pseudomonas spp	Tobramycine	0,112	NA	0,614

NA = non applicable; SCN = staphylocoques coagulase négative; TMP/SMX = triméthoprime-sulfaméthoxazole.
[a]Corrélation positive.
[b]Corrélation négative.

tandis que dans trois autres cas, la corrélation repose sur un décalage de deux années entre la consommation et les résistances. L'utilisation courante de bêta-lactamines en milieu communautaire explique possiblement, en partie, la relation observée entre l'utilisation de certains agents et l'émergence de résistance. De même, nous observons une corrélation positive pour trois couples antibiotique-bactérie en néonatologie soit un couple impliquant la vancomycine, un couple impliquant la cloxacilline et un couple impliquant le méropénem. L'importance relative de la consommation des antibiotiques est à noter. En effet, on constate des corrélations positives pour des niveaux de consommation différents, par exemple la consommation de méropénem est en moyenne de 52,2 JT/1000JP par année en hémato-oncologie et de 10,3 JT/1000JP par année en néonatologie. Dans tous ces cas, ces données exploratoires ne permettent pas d'établir un lien de causalité entre l'utilisation d'un antibiotique et l'antibiorésistance ni de statuer sur la pertinence ou non de décaler les données de consommation et de résistance. Elles illustrent toutefois le lien qui peut exister entre l'utilisation d'un antimicrobien et l'émergence de résistance.

Dans son rapport 2019, le Centers for Disease Control and Prevention américain a commenté l'évolution des résistances aux antibiotiques en comparant les données de 2013 à celles de 2019[25]. Le centre note que la résistance des entérobactéries aux carbapénèmes est stable tandis que la résistance des entérocoques à la vancomycine est en baisse.

En revanche, notre étude met en évidence de nombreux couples bactérie-antibiotique pour lesquels il n'existe pas de lien d'association ou même pour lesquels on constate une corrélation négative. Il est important de rappeler que l'épisode de soins d'un patient constitue généralement une très courte fenêtre de son parcours. La résistance à un antibiotique peut s'installer progressivement et il faut plusieurs

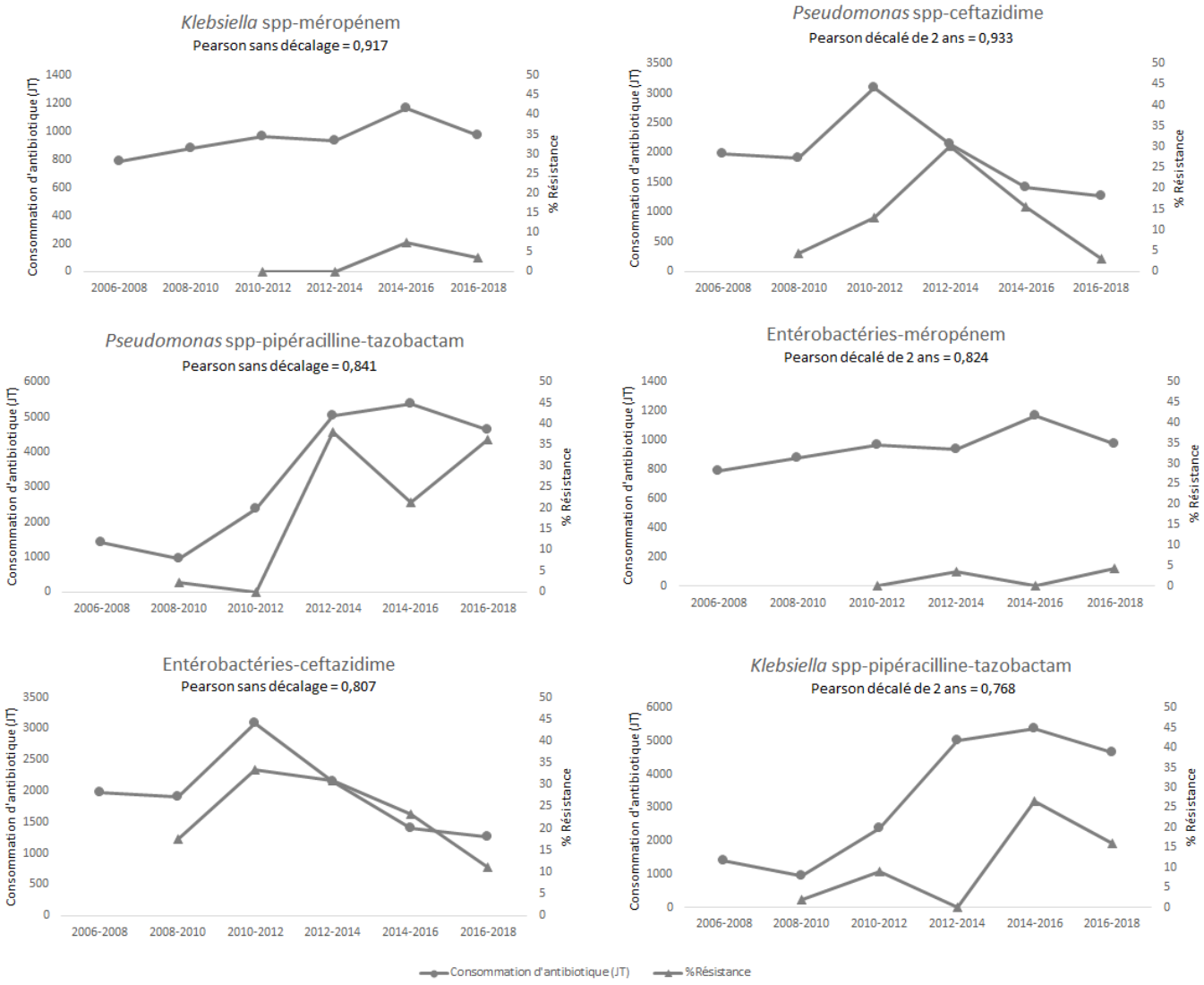

FIGURE 1. Représentation graphique des couples présentant une corrélation positive en hémato-oncologie pédiatrique. JT = nombre de jours de traitement.

années pour être en mesure d'observer une tendance et possiblement un lien entre l'utilisation d'antibiotiques et cette évolution de la résistance. Notre étude décrit une approche exploratoire effectuée dans le cadre de notre programme d'antibiogouvernance. Elle permet aux cliniciens de discuter de l'antibiogramme cumulatif, en mettant en perspective les données d'utilisation. Nous pensons qu'elle contribue davantage à la réflexion et à l'utilisation parcimonieuse de ces antibiotiques.

De façon générale, une corrélation négative représente une hausse de l'utilisation associée à une baisse de la résistance ou encore une baisse de l'utilisation associée à une hausse de la résistance. Dans un contexte exploratoire, ces corrélations négatives ne s'expliquent pas. Toutefois, on peut mentionner que la corrélation négative impliquant les couples *Klebsiella* spp-tobramycine et entérobactéries-tobramycine pourrait s'expliquer par le retrait de cet antibiotique dans l'algorithme de prise en charge de la neutropénie fébrile. Pour les couples SCN-TMP/SMX et SCN-vancomycine, la corrélation négative pourrait s'expliquer par la difficulté de distinguer une réelle bactériémie d'une contamination causée par des germes peu virulents tels que les SCN, dans les cas où une seule hémoculture est prélevée chez les prématurés.

L'approche développée et testée dans cette étude pourrait profiter d'une mise en ligne périodique du profil de consommation et de résistances aux antibiotiques (soit, un antibiogramme cumulatif) dans une base de données en programmant des requêtes permettant de vérifier périodiquement la présence de corrélation. En outre, même s'il n'existe pas de corrélation entre l'utilisation réelle et le taux de résistance pour un couple antibiotique-bactérie, la surveillance du taux de résistance reste incontournable.

Limites

Cette étude descriptive comporte des limites. Les données recueillies portent sur un établissement mère-enfant ciblant deux clientèles pédiatriques. D'autres travaux doivent être menés auprès d'établissements similaires ou comportant d'autres types de clientèles pour généraliser cette approche. Toutefois, même si cette étude montre qu'il est possible d'explorer la relation entre la consommation d'antibiotiques et la résistance, elle ne permet pas d'établir de lien de causalité compte tenu de l'exposition des patients décrits aux antibiotiques en prophylaxie, en traitement ou par l'alimentation. En outre, au cours de leur vie, les enfants ont été moins exposés aux antibiotiques que les adultes. Le profil

TABLEAU 4. Corrélation entre l'évolution de la consommation d'antibiotiques et l'évolution des résistances aux antibiotiques en néonatologie

Bactéries	Antibiotiques	Pearson sans décalage	Pearson décalé 1 an	Pearson décalé 2 ans
E. coli	Ampicilline	0,150	0,138	0,296
E. coli	Gentamicine	−0,218	−0,335	−0,221
E. coli	Méropénem	NA	NA	NA
E. coli	Pipéracilline-tazobactam	0,133	0,477	0,563
Enterobactéries	Gentamicine	−0,119	−0,386	−0,495
Enterobactéries	Méropénem	0,706[a]	0,642	0,127
Enterobactéries	Pipéracilline-tazobactam	−0,154	0,149	0,284
S. aureus	Oxacilline	0,501	0,759[a]	−0,019
S. aureus	Vancomycine	0,465	0,329	0,681
S. epidermidis	Oxacilline	−0,435	−0,467	0,317
S. epidermidis	Vancomycine	0,850[a]	0,488	0,077
SCN	Oxacilline	−0,089	−0,370	0,374
SCN	Vancomycine	0,667	0,159	−0,157
Klebsiella spp	Gentamicine	−0,370	−0,410	−0,629
Klebsiella spp	Méropénem	0,435	0,214	0,556
Klebsiella spp	Pipéracilline-tazobactam	−0,166	0,165	0,179
Enterococcus spp	Ampicilline	0,035	0,071	0,412
Enterococcus spp	Vancomycine	−0,153	−0,257	−0,338

NA = non applicable; SCN = staphylocoques coagulase négative.
[a]Corrélation positive.

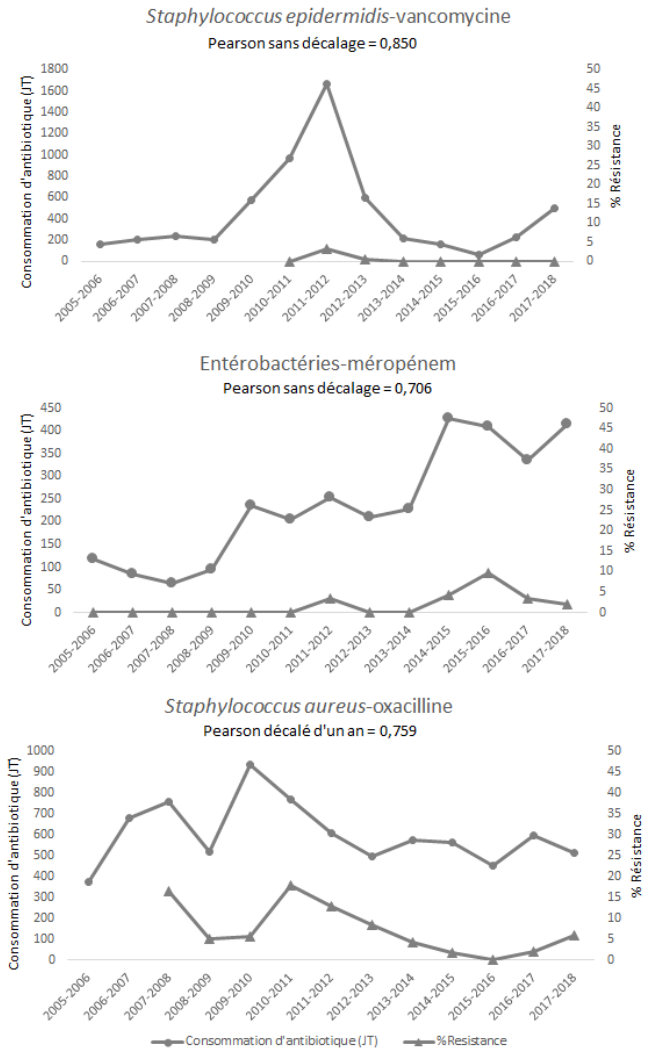

FIGURE 2. Représentation graphique des couples présentant une corrélation positive en néonatologie. JT = nombre de jours de traitement.

des résistances est susceptible de différer d'une étude menée dans un centre hospitalier adulte. Le profil des résistances varie également entre régions et pays.

CONCLUSION

Il est possible d'explorer l'association qui peut exister entre la consommation d'antibiotiques et l'émergence de résistance dans un centre hospitalier universitaire mère-enfant. De tous les couples bactérie-antibiotiques ciblés, notre étude met en évidence une corrélation positive entre la consommation d'antibiotiques et la résistance pour six couples antibiotique-bactérie en hémato-oncologie et trois couples en néonatologie. L'approche exploratoire proposée repose sur un traitement manuel des données. Il pourrait être intéressant d'envisager une approche systématique continue permettant de produire les corrélations de façon automatique.

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Barriers and Facilitators Related to Delivery of Hospital Pharmacy Services to Women, Children, and Their Families during a Pandemic: A Qualitative Study

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ABSTRACT

Background: When the COVID-19 pandemic was declared in March 2020, health care professionals were challenged to adapt quickly and efficiently to change their work practices. However, an evidence-informed approach has not yet been used to systematically gather data on barriers and facilitators related to delivery of hospital pharmacy services in Canada.

Objectives: The primary objective was to identify and describe barriers and facilitators related to the delivery of hospital pharmacy services to women, children, and their families during the COVID-19 pandemic. The secondary objective was to provide recommendations for improvement in delivery of pharmacy services to enhance patient care during pandemics.

Methods: This qualitative study involved semistructured virtual interviews with pharmacists who worked in direct or nondirect patient care throughout the pandemic (since March 2020) at women's and/or children's hospitals in Canada. Individual interviews were completed virtually using conferencing software. An interview guide mapped to the Theoretical Domains Framework version 2 (TDFV2) was used to facilitate the interviews. Interviews were audio-recorded and transcribed verbatim by the principal investigator. Transcribed interviews were coded, mapped to the TDFV2, and analyzed using thematic analysis.

Results: Interviews were completed with 21 pharmacists in 7 provinces across Canada. Barriers and facilitators coded to the TDFV2 were grouped into 4 main themes: communication and collaboration, adaptability, health and well-being, and preparedness.

Conclusions: Participants highlighted a significant number of barriers that they experienced during the COVID-19 pandemic; overall, however, participants reported that they felt prepared for subsequent waves of the COVID-19 pandemic and future pandemics.

Keywords: hospital pharmacy services, COVID-19, pandemic, women's and children's hospitals

Note: This article contains supplementary material (Supplements 1 and 2), available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209.

RÉSUMÉ

Contexte : Lors de la déclaration de la pandémie de COVID-19 en mars 2020, les professionnels de la santé ont été mis au défi de s'adapter rapidement et efficacement à la situation en changeant leurs pratiques professionnelles. Cependant, une approche fondée sur des données probantes pour recueillir systématiquement des données sur les obstacles à la prestation des services de pharmacie hospitalière au Canada et les éléments facilitant celle-ci n'a pas encore été utilisée de manière systématique.

Objectifs : L'objectif principal consistait à identifier et à décrire les obstacles à la prestation de services de pharmacie hospitalière aux femmes, aux enfants et à leur famille et les éléments facilitant celle-ci pendant la pandémie de COVID-19. L'objectif secondaire consistait, quant à lui, à fournir des recommandations pour améliorer la prestation de services de pharmacie afin d'améliorer les soins aux patients pendant une pandémie.

Méthodes : Cette étude qualitative comprenait des entrevues virtuelles semi-structurées avec des pharmaciens ayant travaillé dans le domaine des soins directs ou non directs aux patients tout au long de la pandémie (depuis mars 2020) dans des hôpitaux pour femmes et/ou enfants au Canada. Les entretiens individuels ont été réalisés virtuellement à l'aide d'un logiciel de conférence. Un guide d'entretien adapté de la 2e version du cadre des domaines théoriques (TDFV2) [*Theoretical Domains Framework*] a été utilisé pour faciliter les entretiens. Ceux-ci ont été enregistrés sur bande audio et retranscrits textuellement par le chercheur principal. Les entretiens ainsi retranscrits ont été codés, reportés sur le TDFV2 et analysés par thème.

Résultats : Des entrevues ont été réalisées auprès de 21 pharmaciens dans 7 provinces du Canada. Les obstacles et les éléments facilitateurs codés selon le TDFV2 ont été regroupés en 4 grands thèmes : communication et collaboration; adaptabilité; santé et bien-être; et état de préparation.

Conclusions : Les participants ont mentionné un nombre important d'obstacles qu'ils ont rencontrés pendant la pandémie de COVID-19; dans l'ensemble, cependant, les participants ont déclaré qu'ils se sentaient préparés aux vagues ultérieures de la pandémie de COVID-19 et aux futures pandémies.

Mots-clés : services de pharmacie hospitalière, COVID-19, pandémie, hôpitaux pour femmes et enfants

INTRODUCTION

On March 11, 2020, the World Health Organization declared a global pandemic involving the novel coronavirus SARS-CoV-2, which causes COVID-19.[1] The first case of COVID-19 in Canada was reported in January 2020. By August 2021, more than 1.4 million confirmed cases of COVID-19 had been reported in Canada.[2]

During the COVID-19 pandemic, pharmacists have played an important role in delivering pharmacy services,[3] with community and hospital pharmacy teams becoming actively involved in patient care. In addition, hospital pharmacists have played a key role in completion of clinical trials; generation of evidence-based reviews; development of protocols, clinical order sets, and guidelines; management of drug shortages; and antimicrobial stewardship.[4] A scoping review of pharmacists' response globally to the COVID-19 pandemic highlighted the role of hospital pharmacists in collaboration and teamwork, education, and patient care.[5] Pharmacists have also been acknowledged as key players in the COVID-19 vaccine rollout and in addressing the misinterpretation of vaccine information.[5]

At the same time, pharmacists have faced several challenges in delivering services. In a national survey of community pharmacists conducted by the Canadian Pharmacists Association during the pandemic,[6] respondents reported a variety of challenges, including lack of personal protective equipment, drug shortages, higher workload accompanied by staffing shortages, and increased harassment of staff.[6] However, the experiences of hospital pharmacy teams in Canada were not captured by that survey.

The Canadian Society of Hospital Pharmacists released a statement (in mid-2020) highlighting the important role of the profession and acknowledging the risk to its members in their service to public health.[7] The International Pharmaceutical Federation published a COVID-19 guideline that included responsibilities and roles of hospital pharmacy, such as ensuring adequate supply and procurement of necessary medical supplies and devices, promoting hospital infection control practices, and providing collaborative care.[8] Some of these responsibilities are uniquely challenging for pharmacy teams that provide services to special populations such as pediatric patients and pregnant or lactating individuals. There has been limited evidence available to guide management of COVID-19 in these specific patient populations. Recommendations for COVID-19 vaccination in these populations has been evolving since the vaccines were licensed; vaccination is now recommended for children as young as 5 years of age,[9] and vaccines are deemed safe for use in pregnancy and lactation.[10] Although fewer pediatric patients than adults have experienced hospitalization from COVID-19, some studies have shown that children with chronic diseases are at increased risk for admission to the intensive care unit and mechanical ventilation.[10] Hospital restrictions limiting caregiver support have also been implemented across Canada and may have affected delivery of pharmacy services; for example, pharmacists may have been unable to provide medication counselling to all caregivers who needed it. In addition, pregnant people with COVID-19 are at increased risk for preterm birth, maternal mortality, and preeclampsia relative to pregnant people without COVID-19.[11]

To our knowledge, efforts to systematically gather data about the barriers and facilitators related to delivery of pharmacy services for women, children, and their families using an evidence-informed approach in the Canadian context have not been undertaken. The goal of this study was to better understand the delivery of pharmacy services by hospital pharmacists during the COVID-19 pandemic in Canada. The primary objective was to identify barriers and facilitators related to the delivery of hospital pharmacy services to women, children, and their families. The secondary objective was to provide recommendations for improvement in delivery of pharmacy services to enhance patient care during the COVID-19 pandemic and future pandemics, based on the results of this study.

METHODS

Study Design

This was a qualitative study using virtual interviews to gather opinions and perceptions from Canadian pharmacists.

Development of Interview Guide

The semistructured interview guide was based on the Theoretical Domains Framework version 2 (TDFV2), with the interviews designed to gain understanding of individual-level barriers and facilitators related to behaviour change, which were then linked to the Behaviour Change Wheel (the COM-B model, where "COM" refers to capability, opportunity, and motivation, as explained in more detail below).[12,13] Best practices for qualitative interviewing[14,15] were reviewed, which further aided in creation of the interview questions. The PubMed and Embase databases were searched to identify previous literature related to barriers and facilitators related to delivery of pharmacy services during pandemics. Combinations of the following keywords, including variations on the same terms (e.g., plural and singular), in conjunction with the controlled vocabulary of each database, were used to retrieve articles exploring both community and hospital pharmacy services: "pharmacist", "pharmacy services", "hospital pharmacy services", "clinical pharmacist", "COVID-19", "coronavirus", and "pandemics". The search yielded 51 articles, with an additional 5 articles identified through hand-searching. The report of the Canadian Pharmacists Association survey provided additional context for question development.[6]

The interview questions were developed through the literature search and team discussion. Four semistructured, open-ended interview questions, with example prompts, were mapped to the TDFV2 domains a priori. The team included clinical pharmacists involved in direct patient care and pharmacy practice researchers with experience in qualitative research. In addition, further consultation was held with a qualitative researcher from the Research Methods Unit of Nova Scotia Health.

The 4 interview questions were piloted by the principal investigator (E.R.), by interviewing 5 staff pharmacists who did not meet the study's inclusion criteria. Participants in this pilot project were asked whether the questions and prompts addressed the research question, were well explained, and were detailed enough to capture the intended data. Feedback was encouraged and incorporated in development of the final set of interview questions. Results from the pilot interviews were not included in the study analysis.

Participant Recruitment and Data Collection

Potential participants were licensed staff pharmacists at hospitals for women and/or children across Canada, who were working in at least one direct or nondirect patient care area, to capture different perspectives and experiences, during the COVID-19 pandemic (March 2020 onward).

Potential participants were excluded if they were unable to speak, read, and write in English and if they did not consent to being audio-recorded during the interview.

Pharmacy directors and managers at 14 women's and children's hospitals across Canada (as suggested by the pharmacy director of a local children's hospital), representing all regions of Canada, were contacted by email and asked to disseminate an invitation to participate to pharmacists at their respective institutions. Interested pharmacists then contacted the principal investigator by email. The interview questions (Supplement 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209) and a demographic questionnaire (Supplement 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209) were distributed to participants before the virtual interview. We provided the questions to participants in advance to reduce recall bias.

This study was approved by the IWK Research Ethics Board (REB 1026187). Consent was discussed with and obtained from each participant before the person was interviewed, and participants agreed to be audio-recorded and agreed for anonymous use of direct quotations for presentations and publication of study results. Consent was completed electronically on REDCap, a secure, web-based application (https://www.iwk.nshealth.ca/research/redcap).

At the time of consent, demographic information, including the area of care in which the participant was working, years of clinical experience in a women's and/or children's hospital, and geographic region, was collected electronically on REDCap. The virtual semistructured interviews were conducted through the Webex video conferencing platform (Cisco; https://www.webex.com/) during February and March 2021. The interviews were audio-recorded and transcribed verbatim by the principal investigator, who also completed field notes during the interviews; the field notes were used to record nonverbal communication by and reactions of the participants and to state any biases that the interviewer (i.e., principal investigator) might have had.[16]

Coding and Analysis

NVivo12 software (2018; QSR International Pty Ltd; https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home) was used to facilitate coding of the data. Initial coding was completed independently by 2 team members (E.R., E.K.B.) using the 14 domains of the TDFV2, and was then discussed by the 2 coders. Where consensus could not be achieved, a third team member (J.E.I.) reviewed and provided feedback, which led to consensus. Overarching themes of barriers and facilitators based on the TDFV2 coding were then identified by 2 team members (E.R., E.K.B.) and agreed upon with all members of the team.

Trustworthiness of Data

Various approaches were used to determine and demonstrate the trustworthiness of the data. Before the study interviews began, the research supervisor (E.K.B.) reviewed the audio-recorded pilot interviews and provided guidance on the interviewing process. The interviewer used self-reflective journaling to capture any subjective biases or thoughts throughout the interviews that might have affected the credibility of the analysis process.[16] Anonymous quotes from participants were included in the analysis and this report, to further add to the trustworthiness of the findings and interpretation of the results.[17] Furthermore, 2 team members independently coded each interview, and an audit trail was produced to document the development of codes into categories and themes.[18]

RESULTS

Demographic Characteristics

In total, 21 participants working in 12 tertiary hospitals in 7 provinces were interviewed. Most worked in pediatric direct care (n = 15, 71%), and the mean duration of work experience was 17 years.

Themes

Barriers and facilitators were coded using all 14 TDFV2 domains, but all fell within only 12 of these domains. These 12 domains were then categorized under the following 4 overarching themes (Figure 1): communication and collaboration, adaptability, health and well-being, and preparedness. In the following descriptions of these themes, domains are noted parenthetically. Detailed examples of

barriers and facilitators, with representative quotes, are presented in Table 1. The most consistently discussed domains are outlined in Figure 2.

Communication and Collaboration

Key barriers consistently discussed within the theme of communication and collaboration included virtual care, limited workspace, caregiver and visitor restrictions, student restrictions, and personal protective equipment (PPE) (environmental context and resources; social influences), as well as limited face-to-face interactions (social influences). One participant stated, "Because you have the nursing contracted position presenting at rounds, and then the pharmacy team was trying to interject where they could … I found it very difficult on a virtual interface to make my presence well known" (Participant 8) (environmental context and resources; social influences).

While virtual care was identified as a barrier by some, other participants felt it was a facilitator. For example, one participant said, "They're [the patients] not driving an hour to get to our facility and then back, they just Zoom in then Zoom out for the meeting. So, facilitating care is so much better in the virtual world" (Participant 11) (environmental context and resources).

Adaptability

Adaptability of pharmacists in the workplace during the COVD-19 pandemic was another theme identified. The key barriers discussed in most interviews included confusion associated with rapidly evolving information (memory, attention, and decision processes), stress associated with constant change, increased workload secondary to staff shortages (emotion; environmental context and resources), and the need to adjust to virtual care and changing professional roles (environmental context and resources; social/professional role and identity). One participant stated, "A lot of workload is just because there's so many unknowns and too many policy changes…so I think that was the real stressor, all the changes" (Participant 12) (memory, attention, and decision processes; emotion).

The main facilitators for the theme of adaptability included accessibility of and training in technology and PPE (environmental context and resources; skills). One participant stated, "I also think that we are all more comfortable with all of the technology that we can use, so that also helps, so we understand what some of the different counselling options that we can use are and some of the other workarounds if you can't actually go into the patient's room" (Participant 10) (beliefs about capabilities; skills).

Health and Well-Being

One participant stated, "It's just overwhelming, and it's never-ending, there's just too much going on. There was already too much going on without a pandemic to manage from a workload perspective" (Participant 14) (emotion; memory, attention, and decision processes; environmental context and resources). Barriers that participants reported included increased workload and working hours, as well as the initial conservation and allocation of PPE (environmental context and resources). In addition, the daily stress from increased workload, the unknown, fear of spreading or contracting COVID-19, exhaustion due to constant change (emotion), and limited patient interactions (social influences) were described as barriers.

Key facilitators that participants reported within this theme included feeling like they were helping the collective cause and were a valued part of the team (social/professional role and identity) and coping strategies such as physical exercise (emotion), as well as managerial and co-worker support (social influences).

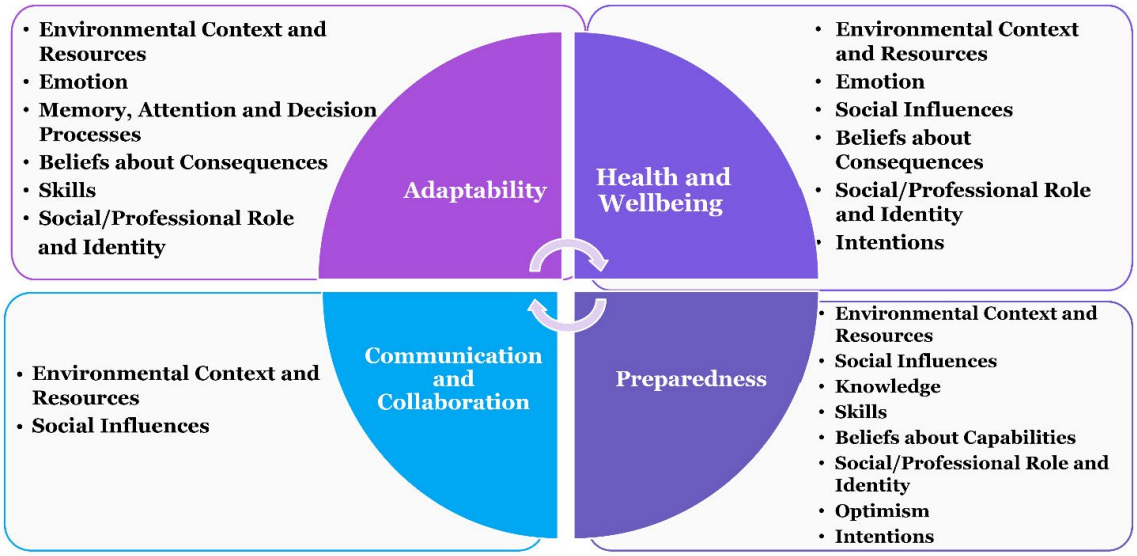

FIGURE 1. Themes (the 4 segments of the graphic) and domains coded within each theme (entries within each segment), based on the Theoretical Domains Framework version 2.

TABLE 1 (Part 1 of 2). Barriers and Facilitators Coded to the Theoretical Domains Framework (Version 2)

Domain	Barriers	Facilitators	Representative Quotation
Knowledge	Initial lack of knowledge about COVID-19 in children and pregnant/breastfeeding women The unknown about the COVID-19 virus	Increasing knowledge about: • Infection control/PPE • Screening protocols • Technology available for patient care • Educational resource changes and procedures (e.g., guidelines, policies) • Transmission of the virus	"So, I think there were so many uncertainties at the start of the pandemic, that it did unfortunately create some barriers in terms of our ability to develop or deliver rather the best pharmacy services possible." (Participant 8)
Skills	Lack of competency and ability to use technology	Experience with the technology used for patient care Skill development for donning and doffing PPE	"You know does everyone have access to the same platforms and does everyone know how to use them?" (Participant 14)
Social/ professional role and identity	Increased responsibilities Decreased scope of practice (e.g., fewer patient interactions) Role changes due to virtual care Professional boundaries	Professional role in prescribing Increased scope of practice (e.g., vaccinations) Planning for role change Role in providing education	"We quickly had to figure out how we were going to do our job, and not even just do our job, but safely provide care which was a real concern because we got so much of our work done on rounds and all of a sudden our job turned into more reactive instead of proactive." (Participant 6)
Beliefs about capabilities	Self-confidence in vaccinating Unfamiliarity and comfort covering different clinical areas	Empowerment in vaccinating Self-confidence in virtual care	"I feel more comfortable now participating in virtual rounds and virtual meetings." (Participant 4)
Optimism	Staff shortages Workspace	Preparedness for another wave Communication with colleagues Vaccinations Knowledge gained from the first wave Plans in place for subsequent waves or pandemics (e.g., policies on PPE and self-isolation, drug shortages, pharmacy scheduling, restricting hospital capacity/ elective surgeries) Managerial staff support	"I think also the communication is much better and more information is available. So, I think we are definitely more prepared." (Participant 7)
Beliefs about consequences	Change in pharmacist's role Virtual care Impact of PPE on communication Staff shortages		"We've had a little less patient contact which is probably one of the major detriments because, unless something is absolutely needed to go speak to patients and families, just to limit contacts and exposure." (Participant 21)
Intentions		Prioritizing work–life balance Planning (e.g., vacation planning, planning for short-staffed situations)	"One thing that I have done is to prioritize my work and the emails that come to me, I'm very selective as to how I manage my emails, because I can't get to them all." (Participant 11)
Memory, attention, and decision processes	Information overload/tiredness Rapidly evolving evidence Loss of focus due to virtual care Fatigue with PPE, planning protocols		"The perpetual and constant changing of information is a lot to process for anybody and we're right there in it. It's just never-ending." (Participant 14)

TABLE 1 (Part 2 of 2). Barriers and Facilitators Coded to the Theoretical Domains Framework (Version 2)

Domain	Barriers	Facilitators	Representative Quotation
Environmental context and resources	Hospital restrictions Workspace and working remotely Students Conservation, allocation, and communication of PPE Scheduling (long shifts) and overwork/understaffing Virtual rounding and patient care (as a resource/IT capability)	Email handover, weekend coverage Daily huddles/communication Impact on communication from management PPOs/policies Virtual care (efficiency)	"I think the biggest barrier was really to just get the whole virtual scheduling and virtual technology in place." (Participant 11)
Social influences	Poor communication because of virtual rounds and PPE Limited face-to-face interactions Hospital restrictions on support people	Structured patient handover	"I would say the first thing was just the visitation policy, that's probably the biggest one. Obviously when you're caring for children that circle of care is a big part of their support system." (Participant 12)
Emotion	Stress from increased workload, change, the unknown, and spreading infection Guilt from neglecting patients Exhaustion from constant change Frustration with technology Stress on families because of hospital restrictions	Coping strategies Resources available to staff (e.g., employee and family assistance program)	"I think it was a bit challenging especially in the beginning, it was new for everyone, everyone was more concerned around being in the hospital environment and I think it was a bit more stressful, getting used to new practices and all of the PPE that you had to wear on a regular basis." (Participant 16)

IT = information technology, PPE = personal protective equipment, PPO = preprinted order.

Preparedness

Overall, there was a consistent perception that individual pharmacy departments and institutions were well prepared for future waves of the COVID-19 pandemic. Key facilitators included confidence in, familiarity with, and training for new processes and technology (knowledge; skills; beliefs about capabilities) and the optimism that comes with having systems in place to deliver care (optimism). Furthermore, managerial support, clarity regarding organizational expectations (social influences), and new roles and responsibilities to fit the restructured work environment (social/professional role and identity) facilitated how participants felt in terms of preparedness. One participant stated, "I definitely think that management has thought about how pharmacy, the profession, can help in terms of managing the second wave or the next waves … once we get through the mass immunization and things move along and if COVID is here to stay … then maybe it'll be another aspect that pharmacists can help with moving forward" (Participant 15) (optimism; social/professional role and identity).

Barriers were drug and staff shortages (environmental context and resources) and pessimism related to staffing and space limitations (optimism). One participant highlighted, "I think we're well prepared, other than we don't have enough staff. That's really the biggest problem we have" (Participant 11) (optimism; environmental context and resources).

DISCUSSION

This study identified perceived barriers and facilitators of hospital pharmacists working in pediatric and women's health care during the COVID-19 pandemic, grouped under 4 main themes. Some of the key barriers identified consistently by participants included the need to adapt to virtual care, increased workload and staff shortages leading to heightened stress at work, and the challenge of keeping up to date with rapidly evolving information. To our knowledge, this is the first study evaluating this research question in a Canadian context. The perceived barriers and facilitators reported by pharmacists in this study can be used by Canadian institutions for future pandemic planning. Despite the barriers identified, most participants remained optimistic and felt well prepared for future waves of the COVID-19 pandemic and subsequent pandemics.

Few studies focusing on the delivery of hospital pharmacy services have been reported in the literature, and we found no studies addressing our specific research question. One survey that explored perceived barriers related to pharmacists' emergency roles during the COVID-19 pandemic was distributed to community and hospital pharmacists and pharmacy students in Jordan.[19] Consistent with our study, pharmacists in Jordan expressed concerns about their new emergency roles and expectations during the pandemic.

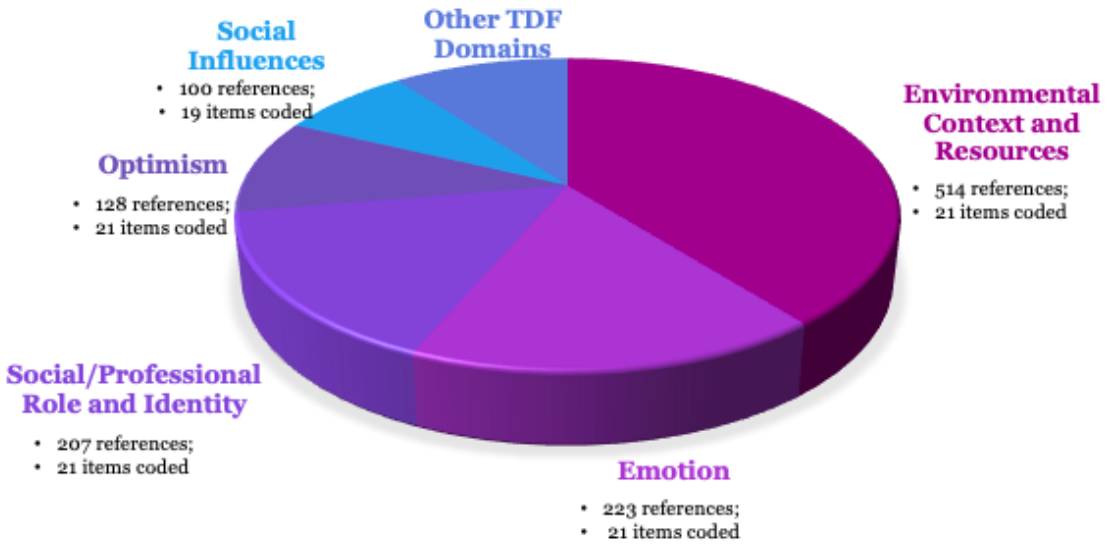

FIGURE 2. References and items mapped to the most commonly identified domains of the Theoretical Domains Framework (TDF) version 2, where "references" means the number of data references coded to the respective domains and "items mapped" means the number of interviews that contained the respective domains.

Pharmacists and pharmacy students responding to the survey believed that pharmacy education providers have a key role in preparing future pharmacists to deal with pandemics.[19] A qualitative study in Saudi Arabia showed an overall positive uptake of nontraditional roles by pharmacists.[20] A Canadian study found that community pharmacists struggled with working longer shifts, which led to emotional overload, but they viewed the scheduling of separate, consistent teams as a facilitator.[21] The barrier represented by longer work hours was consistent with our study. Another similarity between our study and the previous one was the initial challenge with learning new technologies, although technology had an overall positive affect on daily tasks.[21]

Future Pandemic Planning

Identified barriers coded to the TDFV2 can be linked to the Behaviour Change Wheel (or COM-B model) to identify strategies for addressing barriers to future pandemic planning. Based on the COM-B model, the TDFV2 domains are sorted into 1 of 3 factors that need to be present for any behaviour to occur: capability, opportunity, and motivation.[22] These factors can then be linked to intervention functions that can in turn guide the specific strategies that may be implemented to effect behaviour change.[22]

One component of the COM-B that should be targeted is capability.[22] Participants in the current study noted that keeping up to date with new, constantly changing information and adapting to virtual care were major barriers during the pandemic. Strategies that address capability include educational training sessions for various virtual care platforms (intervention function: training) and daily huddles or meetings to keep up to date with rapidly evolving information (intervention function: education/enablement).

Another component of the COM-B model that should be targeted is opportunity.[22] Participants felt that being constantly pulled to different clinical areas and having limited space for learners were barriers during the pandemic. These barriers could be addressed through more cross-coverage training in different clinical areas to combat staff shortages during pandemics, and more training of pharmacists in pediatric and women's health care areas (intervention function: training). Another strategy may be to create more space or reorganize existing space for learners (intervention function: environmental restructuring).

Motivation is the third component of the COM-B model.[22] Participants reported stress associated with increased workload and the unknowns that arose during the pandemic. Strategies such as making mental health resources (such as mindfulness sessions) easily accessible to staff (intervention function: enablement) may be helpful to implement during pandemics.

Some of the above ideas have been brought forward in a new online engagement platform at IWK Health, with the purpose of providing an interactive forum to fast-track innovative solutions in health care.

Strengths and Limitations

To our knowledge, this study is the first to assess individual-level barriers and facilitators experienced by hospital pharmacists working in women's and children's health care institutions in Canada. The qualitative study design allowed collection of detailed information from participants, so the researchers could delve into real-world experiences. The interview guide was reviewed by hospital pharmacists for content and face validity, and was then adapted according to the feedback received. Interviews were coded independently

by 2 research team members to reduce individual-level biases and to increase the trustworthiness of the results. The interviews achieved representation from 7 provinces and 12 different hospital sites across Canada. Although recruitment was a challenge, given the study time frame, regional representation was achieved, as was data saturation, with no new themes being identified in the later interviews. Despite this extent of representation, generalizability of our findings to all hospital pharmacists across Canada may be limited, because the COVID-19 pandemic affected women's and children's hospitals differently from adult institutions. Additionally, interviews were audio-recorded only (without video), which may have limited the observation of participants' nonverbal cues; however, field notes were taken to help in identifying nonverbal cues. Interviews were conducted several months after the first wave of the COVID-19 pandemic, and recall bias may therefore have been a limitation. Lastly, the interviews were completed before the third wave of the pandemic in Canada, which saw significant hospitalizations and deaths nationally. The timing of interviews also preceded mass immunization efforts in most jurisdictions. If follow-up interviews had been completed after these experiences, they might have yielded different results, as roles may have changed during the third wave and in relation to vaccine rollout, with community and hospital pharmacists playing a large role in many jurisdictions.

CONCLUSION

Many barriers to the provision of pharmacy services during the COVID-19 pandemic were identified in this study. Overall, however, participants were optimistic in terms of preparedness to deliver standard pharmacy services during subsequent waves of the COVID-19 pandemic or during other pandemics.

These results have led to recommendations to improve delivery of pharmacy services, which may in turn inform development of policies and initiatives to enhance pharmacy services and patient care during pandemics. Next steps include the implementation of intervention strategies into clinical practice. Future studies may include follow-up interviews with the same study participants after they have experienced additional waves of COVID-19, vaccine rollout, and implementation of the recommended interventions. Additionally, studies examining implementation of the recommended interventions in different patient populations would provide useful information.

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Potentially Inappropriate Prescribing in Hospitalized Older Adult High-Cost Health Care Users: A Pilot Study

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ABSTRACT

Background: High-cost health care users use disproportionate amounts of health care resources relative to the typical patient. It is unclear to what extent poor-quality prescribing, including potentially inappropriate prescribing (PIP), may be contributing to their adverse outcomes and health utilization costs.

Objectives: To evaluate the prevalence of PIP and to explore its impact in older adult high-cost health care users.

Methods: The charts of older adult high-cost health care users admitted to 2 academic hospitals in Ontario, Canada, in fiscal year 2015/16 were reviewed. Eligible patients were at least 66 years old with at least 5 emergency department visits and 3 hospital admissions in the previous year. A total of 243 patients met these criteria, of whom 100 were randomly selected for review. Cases of PIP were identified using explicit prescribing quality indicators, including the STOPP/START criteria. Types of PIP included potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs). Log–linear regression was used to characterize the relationship between PIP and future health care utilization. Medications were reconciled to determine the proportion of PIP addressed by the time of discharge.

Results: Eighty-nine of the 100 patients had at least 1 instance of PIP. In total, 276 PIMs and 54 PPOs were identified. Of the 271 instances of PIP identified on admission, only 38 (14%) were resolved by the time of hospital discharge. Each additional PPO was associated with a 1.43-fold increase in the rate of future emergency department visits ($p < 0.001$).

Conclusions: The rate of PIP among older adult high-cost health care users was high. Despite frequent interactions with the health care system, many opportunities to improve the quality of prescribing for this vulnerable population were missed. Greater attention to medication optimization is needed.

Keywords: older adults, potentially inappropriate prescribing, high-cost health care users, high-need patients

Note: This article contains supplementary material (Supplements 1 and 2), available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209

RÉSUMÉ

Contexte : Les grands utilisateurs de soins de santé consomment une proportion disproportionnée des ressources par rapport aux patients moyens. On ne sait pas vraiment dans quelle mesure la prescription de mauvaise qualité, notamment la prescription potentiellement inappropriée (PPI), contribue aux effets indésirables et aux coûts d'utilisation des soins de santé.

Objectifs : Évaluer la prévalence des PPI et étudier ses effets chez les grands utilisateurs des soins de santé âgés.

Méthodes : Les dossiers des grands utilisateurs de soins de santé âgés admis dans 2 hôpitaux universitaires en Ontario, au Canada, pendant l'exercice 2015-2016 ont été examinés. Les patients admissibles étaient âgés d'au moins 66 ans, avaient effectué au moins 5 visites à l'urgence et avaient été admis 3 fois à l'hôpital au cours de l'année précédente. Au total, 243 patients répondaient à ces critères, dont 100 ont été sélectionnés au hasard pour un examen. Les cas de PPI ont été identifiés à l'aide d'indicateurs explicites de la qualité de prescription, notamment les critères STOPP/START. Les types de PPI comprenaient des médicaments potentiellement inappropriés (MPI) et les omissions potentielles de prescription (OPP). La régression log-linéaire a été utilisée pour caractériser la relation entre la PPI et l'utilisation future des soins de santé. Un bilan comparatif des médicaments prescrits a été effectué pour déterminer la proportion de PPI traités au moment de la sortie de l'hôpital.

Résultats : Quatre-vingt-neuf (89 %) des patients présentaient au moins 1 cas de PPI. Au total, 276 MPI et 54 OPP ont été identifiées. Sur les 271 cas de PPI identifiés au moment de l'admission, seuls 38 (14 %) étaient résolus au moment de la sortie de l'hôpital. Chaque OPP supplémentaire était associée à une augmentation de 1,43 fois du taux de futures visites à l'urgence ($p < 0,001$).

Conclusions : Le taux de PPI chez les grands utilisateurs de soins de santé âgés était élevé. Malgré des interactions fréquentes avec le système de santé, de nombreuses occasions d'amélioration de la qualité des prescriptions pour cette population vulnérable ont été manquées. Une plus grande attention doit être portée à l'optimisation des médicaments.

Mots-clés : aînés, prescriptions potentiellement inappropriées, grands utilisateurs de soins de santé, patients ayant des besoins élevés

INTRODUCTION

In multiple countries, health care utilization and spending are not evenly distributed across the population.[1] High-cost health care users are those individuals who use a disproportionate share of health care resources relative to the typical patient. Although interventions have traditionally focused on acute care, medication optimization represents an area that could potentially improve the overall health of these high-cost users and reduce their health care costs.[2] Studies have shown that prescription medications represent the most expensive category of health care expenditure in the year before a person becomes a high-cost health care user, but it is unclear to what extent poor-quality prescribing, including potentially inappropriate prescribing (PIP), may be contributing to adverse outcomes and health utilization costs.[3,4]

PIP is a significant risk factor for adverse drug events in older adults, with age itself being associated with increased emergency department (ED) visits, morbidity, and health care costs.[5] For the period 2006 to 2011, the Canadian Institute for Health Information reported that 1 in 200 older adults experienced hospitalization related to adverse drug events, compared with a rate of 1 in 1000 younger adults.[6] Appropriate, evidence-based prescribing is essential to achieve better clinical outcomes and value-based care.

PIP can include medication misuse, overuse, and underuse. Misuse or overuse occurs where the harm associated with medication therapy outweighs the benefit and can include drug interactions, duplicate therapeutic classes, or drugs that adversely affect older adults. Underuse occurs where clinically relevant medications without contraindications are not prescribed; this problem may occur more frequently in patients taking a large number of medications.[7]

Given the association between PIP and adverse drug events, and the unclear influence of prescribing quality on the health of high-cost health care users, our objective was to evaluate the prevalence and types of PIP in hospitalized older adult high-cost health care users and to explore the impact of these factors on health care outcomes.

METHODS

We conducted a retrospective chart review of older adult high-cost health care users admitted to medical wards at 2 academic hospitals in Hamilton, Ontario, from April 1, 2015, to March 31, 2016. The Hamilton Integrated Research Ethics Board approved this study.

High-cost health care users were defined as older adults (at least 66 years of age) who had at least 5 ED visits and 3 admissions in the 365 days before the index ED visit. The index ED visit was the last ED visit during the study period. The hospital admission reviewed for purposes of the study was either the admission that resulted from the index ED visit or, if the index ED visit did not result in an admission, the most recent admission preceding the index ED visit. This definition aligns with criteria for high-cost health care users at our local institution and those followed by many other hospital groups. The age cut-off of 66 years was intended to capture individuals eligible for the provincial drug plan. Only patients admitted from the ED were included in the study. An independent statistician randomly selected 100 patients meeting these eligibility criteria for review.

PIP Criteria

The Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) are validated screening criteria that classify PIP as involving either potentially inappropriate medications (PIMs) or potential prescribing omissions (PPOs).[8] Prehospital medications were reviewed against the STOPP/START criteria[8] and 4 additional prespecified PIP criteria (Supplement 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209). We selected the STOPP/START criteria, rather than the Beers criteria for inappropriate medication use in older adults, because evidence suggests that they may better predict adverse drug events and has shown that use of these criteria can decrease adverse outcomes.[8,9] We added the 4 additional criteria to reflect some common, high-priority adverse prescribing practices that have recently become more prevalent in North America, such as high-dose opioid use.[10,11]

Data Extraction

A pharmacist (M.S.) reviewed the medical chart for each selected patient to collect clinical and demographic information (using the data collection form shown in Supplement 2, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/209). If the best possible medication history (BPMH) was not available, information in the chart (e.g., provincial drug reimbursement records) was used to determine home medications. Information in the electronic medical record up to 2 years before admission was used to determine comorbidities and clinical indications for purposes of identifying PIP. For example, absence of renin-angiotensin-aldosterone system (RAAS) inhibitors for patients with heart failure was not considered to represent a PPO if the indication for stopping this type of medication was apparent in the pharmacist's 2-year chart review (e.g., evaluation of patient's renal function, electrolytes, and medical notes). Prehospital medications were reconciled in relation to medications prescribed at discharge to determine the proportion of medications involving PIP that were addressed. The numbers of ED visits and hospital admissions that each patient had after the index admission were collected to determine the association between PIP and future health care utilization.

Pilot Testing and Adjudication

During the calibration phase, 3 investigators (M.S., A.H., J.L.) independently reviewed 5 charts to pilot the chart review process and establish an acceptable level of inter-rater reliability and consistency in identifying PIP. Once the group reached consensus, 1 investigator (M.S.) completed the remainder of the data collection.

Statistical Analysis

We used SPSS (Statistical Package for the Social Sciences, version 20.0 for Windows; SPSS, Inc, an IBM Company) for all descriptive statistical analyses. Log–linear regression models using quasi-Poisson error were applied to describe future health care utilization (R Software, R Core Team [2016], R Foundation for Statistical Computing). The Spearman rho test was used in the post hoc analyses to determine associations between drug classes and future health care utilization. Statistical significance was prespecified by a p value less than 0.05.

RESULTS

Demographic Characteristics

A total of 243 high-cost health care users were identified during fiscal year 2015/16, of whom 100 were randomly selected for review in this study. The mean age was 82.0 (standard deviation [SD] 7.9) years, and 57% were female (Table 1). BPMHs obtained by pharmacy staff were documented in the charts for 27% of these high-cost health care users, and the mean number of home medications was 11.9 (SD 4.4).

Primary Outcome

Eighty-nine of the 100 high-cost health care users had at least 1 medication that involved PIP. In addition, 88 of these high-cost health care users had at least 1 medication involving PIP according to the STOPP/START criteria; as such, the additional PIP criteria (Supplement 1) did not significantly affect the prevalence of PIP. More specifically, 85 and 39 high-cost health care users had at least 1 PIM and at least 1 PPO, respectively. The mean numbers of potentially inappropriate prescriptions, PIMs, and PPOs were 3.7, 3.2, and 1.4 per patient, respectively.

Table 2 lists the most frequent PIMs and PPOs. Among the 276 PIMs, medications without an evidence-based indication were the most frequently identified (n = 115, 42%), and docusate and natural health products accounted for 20 and 24 of these PIMs, respectively. Among the 54 PPOs, the absence of RAAS inhibitors for patients with reduced ejection fraction heart failure or coronary artery disease was the most frequently identified (n = 20, 37%). The therapeutic classes most frequently implicated in PIP for high-cost health care users were anticoagulants and antiplatelet agents, RAAS inhibitors, benzodiazepines, opioids, and stool softeners.

Secondary Outcomes

According to the log–linear regression model with quasi-Poisson error, PPOs were a significant predictor of ED visits in the next year ($p < 0.001$), but not future hospitalizations ($p = 0.06$). Each additional PPO was associated with a 1.43-fold increase in the rate of future ED visits ($\beta = 0.34$, $p < 0.001$). PIP and PIMs were not a predictor of either ED visits or hospitalizations.

Post hoc multivariate analyses were conducted to determine associations between individual medications involving

TABLE 1. Baseline Characteristics

Characteristic	% of Patients[a] (n = 100)
Age (years) (mean ± SD)	82.0 ± 7.9
Sex, female	57
Living situation	
Home	76
Retirement or nursing home	24
No. of home medications (mean ± SD)	11.9 ± 4.4
Serum creatinine on admission (mmol/L) (median and IQR)	106.1 (70.7–176.8)
eGFR (mL/min/1.73 m^2) (median and IQR)	55 (32–84)
Method of medication reconciliation	
BPMH	27
Other	73
Past medical history	
Hypertension	91
Ischemic heart disease	67
Peripheral vascular disease and atherosclerosis	58
Congestive heart failure	51
Cardiac arrhythmias	50
Cancer	42
Arthritis and related disorders	41
Gastroesophageal reflux disease	40
Diabetes	39
COPD	31
Most responsible diagnosis	
Urinary tract infection	12
Heart failure exacerbation	11
Pneumonia	9
COPD exacerbation	8
Ischemic heart disease	7
Sepsis	4
Cancer	4
Renal failure	4
Syncope	4
Other	41

BPMH = best possible medication history, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range, SD = standard deviation.
[a]Except where indicated otherwise.

TABLE 2. Most Frequently Identified Types of Potentially Inappropriate Prescribing

Medication	No. (%)
Potentially inappropriate medications	*n* = 276
Any drug prescribed without evidence-based clinical indication	115 (42)
Concomitant use of drugs that interact pharmacodynamically with oral anticoagulants or antiplatelet agents to increase risk of bleeding: • Other oral anticoagulants or antiplatelet agents • Selective serotonin reuptake inhibitors • Select antibiotics (interaction with warfarin only) • Amiodarone (interaction with warfarin only) • NSAID	16 (6)
Benzodiazepines (sedative; may cause reduced sensorium or impair balance)	14 (5)
Benzodiazepines for ≥ 4 weeks	14 (5)
Use of high-dose opioids (dose ≥ 50 mg/day morphine equivalent)	10 (4)
Concomitant use of at least 2 of the following: opioids, benzodiazepines, alcohol	9 (3)
ACE inhibitor or ARB for patient with hyperkalemia	7 (3)
Potential prescribing omissions	*n* = 54
ACE inhibitor or ARB for patient with congestive heart failure and/or documented coronary artery disease	20 (37)
Bone antiresorptive or anabolic therapy for patient with documented osteoporosis (BMD T-score below –2.5 at multiple sites), where no pharmacological or clinical status contraindication exists, and/or previous history of fragility fractures	9 (17)
β-Blocker for patient with ischemic heart disease	6 (11)
Vitamin D supplementation for older patient who is housebound or is experiencing falls or has osteopenia (BMD T-score between –1.0 and –2.5 at multiple sites)	4 (7)
Vitamin D and calcium supplementation for patient with known osteoporosis and/or previous fragility fractures and/or BMD T-score below –2.5 at multiple sites	3 (6)
Antiplatelet therapy for patient with documented history of coronary, cerebral, or peripheral vascular disease	3 (6)

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMD = bone mineral density, NSAID = nonsteroidal anti-inflammatory drug.

PIP and future health care utilization. Using the Spearman rho test, high-dose opioid use was weakly associated with increased ED visits ($\rho = 0.283$, $p = 0.015$), but not hospitalizations.

Thirty-eight (14%) of the 271 instances of PIP in 77 high-cost health care users had been addressed by the time of hospital discharge: more specifically, 17% (37/223) of PIMs were discontinued, and therapy was initiated for 2% (1/48) of PPOs.

DISCUSSION

High-cost health care utilization and PIP are major public health issues facing older adults. In our study, PIMs involving anticoagulants and antiplatelet agents, opioids, benzodiazepines, and docusate, along with PPOs involving RAAS inhibitors, were the most common. The Institute for Safe Medication Practices (US) and the Institute for Safe Medication Practices Canada have designated opioids and anticoagulants as high-alert medications and antiplatelet agents as high-alert medications in older adults,[12-14] so these medications may represent priority areas to target for improvement efforts, given their prevalence, clinical importance, and potential risks. Although docusate is unlikely to contribute to negative outcomes, it still contributes to wasted resources and represents a missed opportunity to prescribe more evidence-based laxatives.[15]

The prevalence of PIP in this study was higher than in other studies that have applied the STOPP/START criteria.[16,17] There could be several contributory factors. First, previous studies were conducted in general populations, whereas we studied older adult high-cost health care users, who represent a distinct population that may have higher rate of PIP. Our population appeared to be in worse health, as illustrated by 23% of the patients dying in hospital or being transferred to palliative care by the time of discharge, similar to other studies evaluating high-cost health care users.[1] This status may have contributed to the higher number of medications involving PIP that we observed.

In this study, only PPOs were associated with increased ED visits (on the basis of modelling). However, given that

the quasi-Poisson test is conservative, the study might not have had the appropriate sample size and power to demonstrate a relationship between PIP and future health care utilization. In addition, health care utilization among high-cost health care users is likely multifactorial and may not be explained solely by PIP.

Our study suggests that there are missed opportunities to optimize medication therapy for high-cost health care users, despite their frequent exposure to health care settings and providers. Factors such as administrative pressures, high patient load, and hesitancy to change long-term medications may be contributing to these missed opportunities. Further exploration is required to determine the significance of these factors.[18]

This study had some limitations. Generalizability may be limited because of the sample size and geographic setting (a single municipality). There may be potential inaccuracies, given that only 27% of the patients had a BPMH gathered prospectively during their admission; for the remainder of patients, a pharmacist determined the BPMH retrospectively during data collection, including reviewing scanned admission notes and progress notes. Despite the low rate of BPMH at the time of admission, many patients had their medication history documented by other medical professionals, such as physicians and medical clerks. Some of these medication histories may have met the criteria for a BPMH; however, unlike those completed by pharmacy staff, such histories are not routinely labelled as such in the electronic medical record. It is also possible that some PIP that we identified was appropriate, but supporting justification was not evident in the 2-year historical chart review.

To the best of our knowledge, no previous study has analyzed prescribing patterns among older adult high-cost health care users, and thus our findings have implications for future research. In our study, most medication therapy for high-cost health care users was not optimized, and minimal interventions were done during hospital admissions. Opioids, anticoagulants, and antiplatelet agents may represent high-yield areas where targeted interventions can significantly affect outcomes. Given the complexity of medical conditions and required care for high-cost health care users, an interprofessional team with unique clinical expertise should collaborate to optimize their management.

CONCLUSION

In this pilot study, the care of older adult high-cost health care users was not optimized in terms of evidence-based use of medications, and rates of intervention during hospital admissions were low. Larger studies are required to determine the clinical significance of inappropriate prescribing and whether targeted interventions to optimize medication therapy for these high-cost health care users will improve clinical outcomes or reduce health care costs. Certain classes of medications, including opioids, anticoagulants, and antiplatelet agents, may be high-yield areas for targeted interventions.

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Drug Optimization, Sustainability, and Evaluation (DOSE) Project in Alberta Health Services

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INTRODUCTION

Before amalgamation into Canada's first province-wide, fully integrated health system in 2009, Alberta Health Services (AHS) used a decentralized approach for the allocation and management of positive and negative variances in drug budgets and expenses to individual patient care areas in 12 separate health entities. With amalgamation, the former pharmacy departments were merged into the AHS Pharmacy Services program, and in 2012 drug budgets were centralized under this program, in an attempt to find efficiencies and cost savings. However, cost and utilization data continued to be spread across 5 unlinked systems, with no standardization of workflows, vocabulary, or types of data captured, and many hours of labour were required to manually gather and consolidate needed information. As such, it was soon realized that better understanding and reporting of drug utilization would facilitate improved financial stewardship of drug resources. Therefore, in 2013, AHS Pharmacy Services collaborated with the AHS Finance and Enterprise Business Intelligence departments on a project to create a data warehouse that would encompass information about drug utilization, prescribing, and expenditure, as well as patient and program information. The goal was to establish the foundation for a data-driven, evidence-based program that could be used to more effectively manage the provincial drug budget and address the full scope of pharmacy-related analytics within the health care organization. Six years later, the innovative DOSE (Drug Optimization, Sustainability, and Evaluation) data warehouse and phase 1 dashboards were ready for use by AHS leaders and staff.

DESCRIPTION OF THE PROJECT AND PROGRAM

The DOSE team consisted of more than 40 leaders and technical staff drawn from AHS Pharmacy Services, Analytics, and Information Technology (IT). Business and project plans were developed and approved, with each department contributing necessary resources for the endeavour.

The team started by gathering and analyzing data from each individual pharmacy information system (i.e., Meditech [Medical Information Technology, Inc], BDM [BDM Healthware Inc], Millennium PharmNet [Cerner], VAX [AHS]), and the purchasing/financial system (i.e., Oracle EBS [Oracle Corporation]) to determine which elements would fit the business requirements; these data were also assessed for information quality. Extracted data elements encompassed medication orders, medication dispensations, inventory transfers, drug catalogues, and purchase receipts. Data were extracted from each source system and were then consolidated and conformed to common provincial standards; this step was accomplished by means of 16 master reference tables, as required and as feasible, using Informatica software. One key master reference table was created for drugs, based on the Health Canada Drug Product Database.

An iterative process was used to develop various information products, incorporating feedback from stakeholders. Existing software infrastructure was leveraged, including the PowerDesigner modelling tool (from Sybase Inc), the PowerCenter for extract, transform, and load processing, and Analyst for data quality (both from Informatica). A total of 682 source pharmacy data elements were validated and consolidated into 376 data elements in 3 final views (i.e., medication orders and dispensations, drugs, and inventory transfers), which were then displayed as "dashboards" using software from Tableau Software, LLC (Figure 1). Metadata were documented and training resources developed for IT analysts to understand how to extract and use the data in response to various requests, including research and quality improvement projects. To comply with privacy requirements, a built-in auditing capability was set up to monitor access and use of the data. As the business owner, AHS Pharmacy Services maintains and governs access to the data.

The DOSE data set conforms data from 2012 to the current state; the data are obtained from 454 provincial sites and are updated daily. The data set represented an initial volume of 650 million records at completion of phase 1 in

2019, and the plan is to add roughly 100 million new records annually thereafter. Eight base dashboards were created for inventory transfer data: 1 database contains summary data, 1 database contains data related to financial coding, 3 databases are tied to formulary status, and 3 databases are based on geography (Figure 2). These dashboards can be filtered by date, site, zone, drug, dosage form, program, patient type, or unit. The dashboards are updated monthly. Future project phases include the creation of additional dashboards for ordering and dispensing information (Figure 3).

EVALUATION OF THE PROGRAM

The DOSE project was evaluated in the following ways: data quality, project management evaluation, and number of points of access by individual users.

Data Quality

User acceptability testing was accomplished by asking members of the DOSE working group to answer a series of drug use and evaluation questions using the legacy pharmacy or financial systems versus DOSE. Results were compared by the working group chair, and any discrepancies were investigated to determine the cause. For questions related to numeric values, responses from the legacy and DOSE systems matched perfectly. Mismatches were found in answers to questions about top drugs by expenditure at individual sites; causes of discrepancies were further investigated and remedied if possible.

The following are examples of drug use and evaluation topics relevant to the project objectives:

- Most current utilization and cost implications of the AHS initiative for streamlining use of low-molecular-weight heparin are easily accessible to users within 10 minutes, with the ability to drill down to the data for individual sites and units and to show the effects of procurement interruptions (Figure 4).
- Expenditure reporting for the top 25 formulary and nonformulary drugs, which was previously done by 5 staff members over 11 working days, can now be done by 1 staff member in 0.5 day.
- Collection of drug information regarding amphotericin B utilization to inform clinical practice within and order set creation by the provincial hematology-oncology program, which formerly required 4 staff working for a total of 5.4 days, can now be completed by 1 pharmacist in a single day.

Project Management Evaluation

In July 2019, the remaining 39 members of the project team (including 16 [41%] from Pharmacy Services, 2 [5%] from IT, and 18 [46%] from Analytics) were surveyed. Of the 18 respondents (46% response rate), all felt that the meetings were either usually or always a valuable use of time and

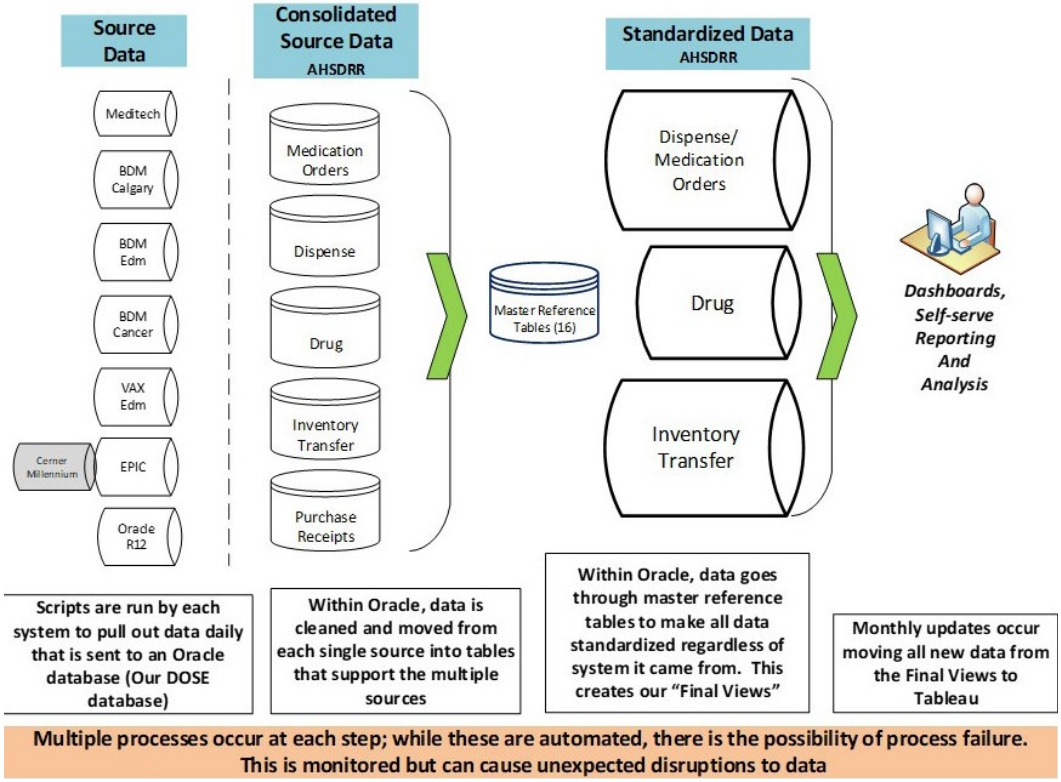

FIGURE 1. Schema for data flow from source systems to DOSE warehouse to DOSE dashboards. DOSE = Drug Optimization, Sustainability, and Evaluation project.

that overall the time dedicated to the project was well spent. Fifteen (83%) felt that the right people had been assigned to the project; 16 (89%) and 17 (94%) of respondents thought that communication from Analytics was effective and timely, respectively; and all respondents agreed or strongly agreed that they knew where to go with questions.

FIGURE 2. Example of dashboard for the Drug Optimization, Sustainability, and Evaluation (DOSE) project.

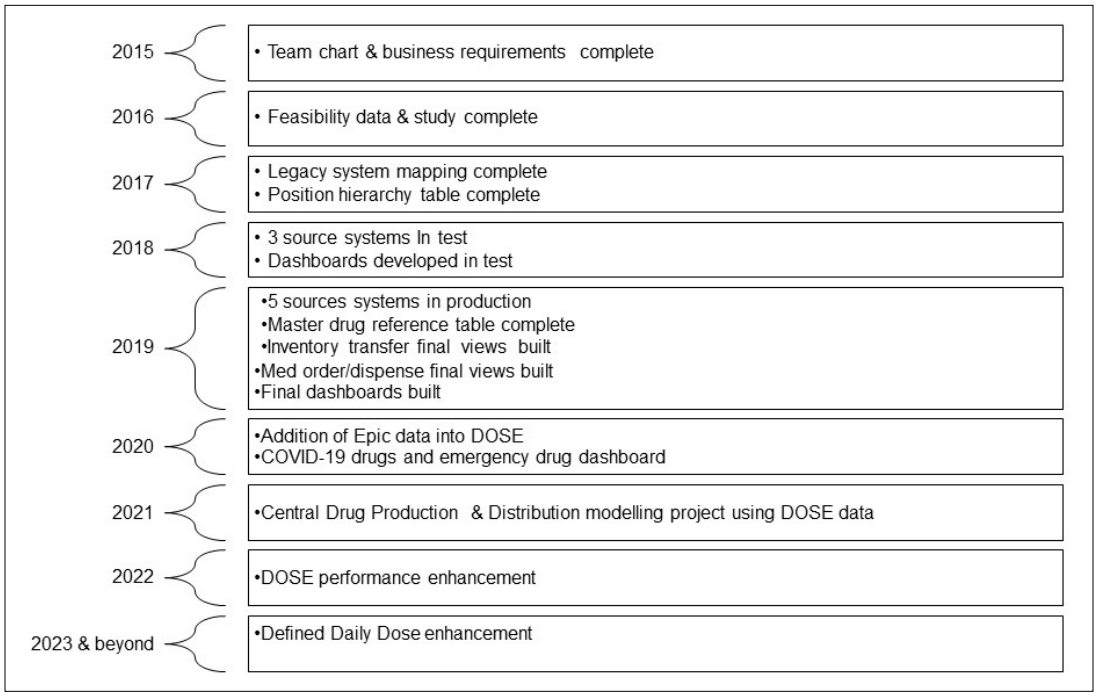

FIGURE 3. Major milestones achieved during the Drug Optimization, Sustainability, and Evaluation (DOSE) project.

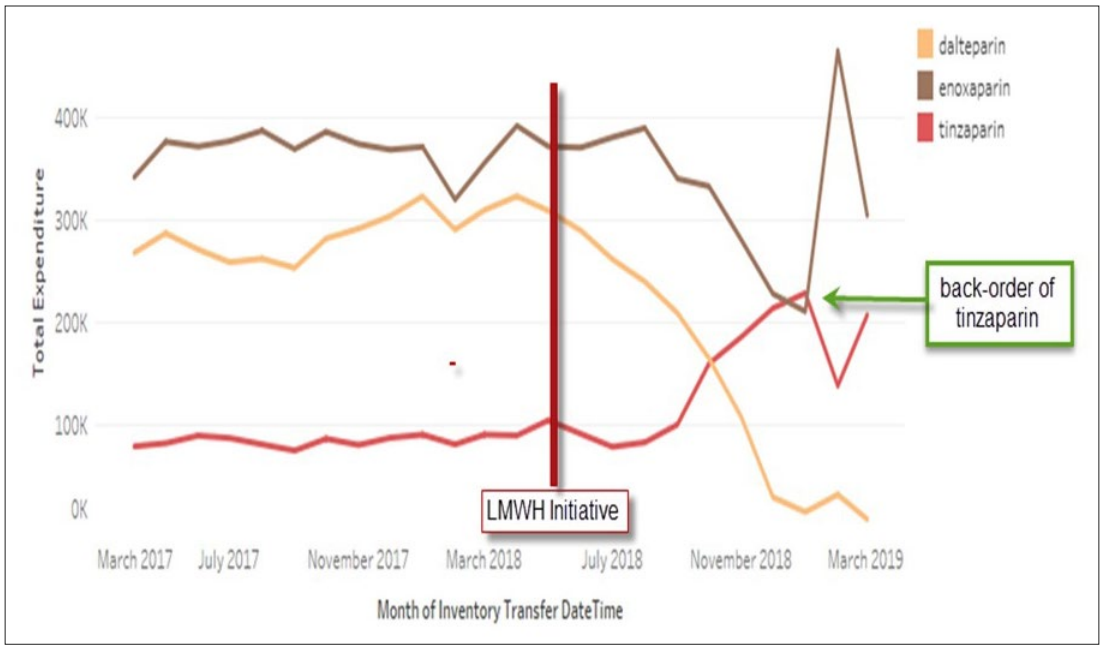

FIGURE 4. Dashboard for the Drug Optimization, Sustainability, and Evaluation (DOSE) project, showing the effect of low-molecular-weight heparin initiative on expenditures for dalteparin, enoxaparin, and tinzaparin over 2 years.

Continued Use

Since launch of the dashboards, their utilization has grown substantially, to totals of 80 users and 2040 hits by September 2021. Daily average hit counts have increased from 9 to 14. The top 3 users accessed DOSE between 211 and 278 times, averaging 0.88–1.16 times per day, based on 240 worked days per year.

CHALLENGES

The DOSE project was large in scope and resource requirements, because of the amount and types of data being extracted. Half of the post-project survey respondents felt that more time had been spent on the project than originally anticipated because of its complexity. As well, 7 (39%) of the respondents felt that those assigned to the project had been allowed insufficient time to complete the work.

The initial business plan estimated project completion in 23 months, with 11.75 full-time equivalents (FTEs); in reality, however, the project required 78 months and 25.03 FTEs. One contributing factor may have been the difference in priority assigned to the project by different teams. For example, DOSE was regarded as high-priority work within Pharmacy Services, whereas for IT, it was considered a low priority.

As well, significant changes in medication management occurred over the course of the project, which affected data outputs. For example, the Alberta College of Pharmacy mandated compliance with USP General Chapter <797> standards for compounding and repackaging of sterile and nonsterile products by 2021, which led to less batching and fewer products made by nurses and a corresponding change to expenditures for drugs, supplies, and wastage; these adjustments created additional challenges for data analytics. In addition, the need to wait for source system data and to address competing project priorities added to the overall time required for the DOSE project.

Data quality issues identified in the source data were due to errors in recording purchases and vendor delivery, as well as delays in receiving credits, other accounting problems, and user errors, similar to other data reported from warehouse builds.[1-6] Attribution of drug costs and use to the appropriate clinical service was a problem because the computer systems were not completely synchronized with patient movements and not all patient orders were entered in the pharmacy information systems. It was assumed that the attribution errors evened out over time, and these were not further addressed; however, the true extent of the contribution of these errors will be seen as a single provincial clinical information system is rolled out to all of AHS in future years.[2] A large number of null expenditures have appeared in the DOSE data set, where financial data cannot be mapped to a corresponding functional centre. This problem will be addressed through the current data quality project in AHS.

IMPLICATIONS AND SIGNIFICANCE FOR PRACTICE

DOSE was the first large-scale informatics project undertaken by AHS Pharmacy Services, and many lessons were learned throughout the process. Allocating dedicated project resources, designating a project manager, and seeking buy-in from senior leaders were key, especially given that during

the course of the DOSE project, the province embarked on another, even larger electronic clinical information system project (called Connect Care) to house all AHS, partner, and affiliate medical records and information. As well, the initial plan to build core data tables one source system at a time was abandoned when it was realized that working on one table for all systems at the same time was more beneficial, because it prevented re-work. Also, more thorough investigation and understanding of site practices at the time of project initiation would likely have helped to identify additional unanticipated complexities in standardization, which hindered the team's ability to learn and improve the efficiency of the product build.

Although the main objectives of the DOSE project were related to drug utilization and cost implications, other, unanticipated uses have emerged:

- Drug record build for implementation in the Connect Care system
- Financial costing of drug budgets for novel clinical programs
- Creation of dashboards for COVID-19 and other pandemic medications, to help monitor and manage drug shortages
- Creation of a dashboard for wastage for AHS Pharmacy Services in the Calgary zone, which allows improvement in the process for managing cumulative expenses due to drug and supply wastage[3]
- Reporting of utilization of naloxone kits and suboxone for provincial harm reduction and opioid crisis initiatives
- Utilization data to help guide sites applying for Choosing Wisely Canada level 1 designation

More generally, DOSE is able to perform activities that are impossible for other data warehouses and applications described in the literature,[2] as summarized in Table 1.

CONCLUSION

Projecting future drug expenditures is difficult. Demographic, economic, and political conditions, as well as technological innovations, influence the use and price of medications. To effectively budget and manage expenditures, leaders need to be aware of the drivers of medication use and spending. Historically, a variety of portfolios within AHS Pharmacy Services have largely used manual, labour-intensive processes to obtain the information needed

TABLE 1. Comparison of DOSE with Other Data Warehouses and Applications

Topic	Other Data Warehouses or Applications[7]	DOSE	Benefits of DOSE
Data access and availability	Use of data in cost-accounting and purchasing systems only	Use of inventory transfer and medication order dose information	Prevent inaccuracies or gaps in drug use data
	Data typically from only a few sites	Data from 454 sites	Improved generalizability
	Use of claims data for public drug programs for patients in the community (e.g., in the United States, IQVIA National Sales Perspective database; in Canada, the National Prescription Drug Utilization Information System)[8] Data for hospital drug expenditures on specific drugs or drug classes lacking and difficult to find	Use of hospital drug expenditure and utilization data from a large health region	Ability to merge inpatient and outpatient drug databases to view costs from perspective of an integrated health system More accurate, ICD-9-driven, disease-based benchmarking of clinical practices within and external to AHS to identify best practices or measure specific outcomes for specific patient subtypes
User requirements	Requirement for specialized knowledge and skills to produce reports	Autogeneration of reports	Improved accessibility and timeliness of reports
System requirements and capabilities	Extraction of large data sets may affect system performance	External server and dedicated analysts	No effect on performance of source system
	Limited product information in summary form or large, unwieldy, unstandardized data components	Merger of similar products into one line item or breakout details on individual dosage forms	Improved identification of treatment variability among programs, sites, or units Easier cross-linking of pharmacy data with ICD-9 disease states/codes Improved standardization of cost-effective and clinically superior care

AHS = Alberta Health Services; DOSE = Drug Optimization, Sustainability, and Evaluation project; ICD-9 = International Classification of Diseases, Ninth Revision.

for drug budget forecasting and expenditure reports. The DOSE data warehouse and associated dashboards now offer a quick visual tool based on existing data to monitor performance and metrics and can help to quickly uncover any potential problems and guide more immediate action to remedy them.[3]

Although it is a powerful tool, DOSE is only one piece of the equation for improving drug use and evaluation by pharmacies. The technology enhancements must be accompanied by corresponding supports if desired outcomes are to be achieved. These outcomes include promoting a culture of process improvement and quality assurance for patient safety and change management strategies.[5] Although the AHS organization as a whole and Pharmacy Services more specifically already have this type of supporting infrastructure in place, more consistent application, along with use of various DOSE tools, could dramatically improve the development, implementation, and reinforcement of large-scale drug stewardship initiatives for even more cost savings and efficiencies.[9,10]

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Potassium Supplementation to Prevent Severe Hypokalemia and Paralysis after High-Dose Methylprednisolone for Ophthalmopathy in Uncontrolled Graves Disease: A Case Report

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INTRODUCTION

Graves disease, the most common cause of hyperthyroidism, is an autoimmune disorder in which thyroid-stimulating immunoglobulins or thyroid-stimulating hormone receptor antibodies cause excessive production and systemic release of thyroid hormones.[1] Common pathognomonic signs include diffuse goitre and ophthalmopathy. The latter will manifest in 25%–40% of patients affected with Graves disease.[1,2] Symptoms usually include inflammation, exophthalmos or periorbital edema, blurred vision, diplopia, and reduced perception of colour. The treatment of ophthalmopathy will depend on its severity, the goal being to preserve sight.[1,2] Conservative treatment with topical lubricant to maintain moisture of the ocular surface and restoration of euthyroidism is recommended for patients with mild to moderate symptoms. In severe cases, IV corticosteroids are considered the mainstay of treatment.[2] The standard regimen is usually methylprednisolone 500 mg IV weekly for 6 weeks, followed by 250 mg weekly for another 6 weeks. Higher doses can be used in more severe cases.[3]

Serious adverse effects associated with the use of high-dose corticosteroids in uncontrolled Graves disease include hepatic toxicity, cardiovascular and cerebrovascular events, and rarely thyrotoxic periodic paralysis (TPP). TPP is characterized by the abrupt onset of severe hypokalemia-induced paralysis, with a reported incidence of approximately 2% in Asian populations and an uncertain incidence in Western populations.[4,5] The proposed mechanisms for this reaction are associated with increased expression and activity of sodium–potassium (Na/K) ATPase by both glucocorticoids and thyroid hormones, leading to intracellular shift as well as renal excretion of K.[6] Other mechanisms potentially contributing to an increase in Na/K ATPase activity are an increase in the number and sensitivity of β receptors, which causes catecholamine-mediated K uptake, as well as an increase in androgen levels, the latter being characteristically seen in males.[5,7] Notably, TPP can occur in a thyrotoxic state with or without administration of glucocorticoids, and it is usually reversible with K supplementation.[7-9] It is unclear whether pre-emptive K supplementation and close monitoring of K levels following high-dose corticosteroid use could be beneficial to prevent this adverse event.

We present here a case of severe hypokalemia and paralysis following the use of high-dose methylprednisolone for treatment of ophthalmopathy associated with uncontrolled Graves disease, in which K supplementation was pre-emptively added for the rechallenge.[3]

CASE REPORT

A 29-year-old Thai man presented to the emergency department for bilateral lower-extremity paralysis and bilateral upper-extremity paresis.* Three days before the emergency department visit, Graves disease with diplopia and moderate to severe ophthalmopathy had been diagnosed. At the time of diagnosis, free thyroxine (T4) was 50.2 pmol/L (normal range 8–20 pmol/L), thyroid-stimulating hormone was less than 0.01 mU/L (normal range 0.38–5.33 mU/L), and serum K was 4.4 mmol/L. He had no prior history of chronic illnesses and did not take any medications. He had started therapy with oral methimazole and propranolol.

For the ophthalmopathy, the patient was scheduled to receive methylprednisolone 500 mg IV weekly for 6 doses, then 250 mg weekly for 6 doses (the standard regimen). One day before the emergency department visit, he received his first dose of methylprednisolone at 0900. No reaction occurred during the infusion. At midnight, he experienced

*The patient provided verbal consent for publication of this case report, in accordance with hospital regulations, and his consent was documented in the medical file.

sudden and brief paralysis of his lower extremities while walking, which led to a fall. The paralysis resolved after a few minutes, and he was able to get up and go back to bed. When he woke up the next morning, at 1100, his lower extremities were paralyzed, and his upper extremities were limited in flexion. Emergency services were called, and he was brought to the emergency department that afternoon. Internal medicine and endocrinology were consulted. Laboratory examination showed that serum K level was 1.9 mmol/L and serum creatinine kinase 559 U/L (normal range 30–213 U/L). The results of all other laboratory investigations, including renal function, were normal. Neuromuscular examinations showed lower limb symmetry. He was given potassium chloride (KCl) as an IV bolus (10 mEq over 1 hour), followed by an IV drip (KCl 40 mEq/L at a decreasing infusion rate over 16 hours). His serum K returned to normal, and the paralysis and weakness resolved in less than 24 hours, with no other recurrence.

The patient was scheduled for a rechallenge with methylprednisolone 500 mg IV on an internal medicine unit 1 week later, with planned oral K supplementation. Before the rechallenge, serum K was 3.4 mmol/L and creatinine kinase 43 U/L. T4 was 16.3 pmol/L and thyroid-stimulating hormone less than 0.01 mU/L. The first planned 20 mmol oral KCl tablet was given at the beginning of the infusion. Four hours later, serum K was 4.6 mmol/L, at which time the second planned 20 mmol oral KCl tablet was given. An additional dose of 20 mmol was prescribed to be given the same night, about 11 hours after the start of the infusion. An hour after the last KCl dose, serum K was 4.7 mmol/L. The next day, serum K was 4.3 mmol/L at 0700 and 3.7 mmol/L at 1200 (noon). The patient was discharged with a prescription for K 20 mEq oral tablets to be taken at 1000, 1500, and 2200 on the days of methylprednisolone administration. He was able to complete the treatment without recurrence of TPP or other adverse effects.

DISCUSSION

This report describes a patient with uncontrolled Graves disease who presented with paralysis of the lower extremities and paresis of the upper extremities associated with severe hypokalemia following administration of high-dose methylprednisolone, who received pre-emptive K supplementation for the rechallenge. The administration of methylprednisolone was considered safe with planned oral KCl supplementation consisting of 3 separated doses of 20 mmol each, given over a period of 12 hours around the infusion. A Naranjo score of 6 was obtained for this case, indicating probable causality between administration of methylprednisolone and onset of severe hypokalemia in the context of hyperthyroidism as seen in Graves disease.

Similar cases have been described in the literature.[10-12] Most of these involved young men of Asian descent presenting to the emergency department with abrupt onset of severe paralysis of the lower limbs or all limbs. Laboratory investigations revealed underlying uncontrolled thyrotoxicosis and severe hypokalemia resulting in the diagnosis of TPP, which likely also explains this patient's severe hypokalemia-related paresis.

TPP is due to a transcellular K shift related to increased Na/K ATPase activity in skeletal muscle, due to direct stimulation by thyroid hormone. However, history of the present illness in this patient revealed prior administration of high-dose IV glucocorticoids within 24 hours of symptom onset, which could also have induced hypokalemia-related paresis. Interestingly, glucocorticoids may also increase the Na/K ATPase pool, through steroid-induced hyperinsulinemia (which also stimulates Na/K ATPase action), and by increasing renal K loss.[6] The combination of these mechanisms may explain the severity of the hypokalemia observed in this case. In fact, this hypothesis is supported by the maintenance of normal serum K levels despite rechallenge with high-dose IV corticosteroid by pre-emptive KCl supplementation and a concurrent decrease in T4 levels following methimazole initiation.

Despite the rarity of TPP, health care providers should keep it in mind as a possible complication of Graves disease, and should be aware that concurrent high-dose methylprednisolone administration could further increase the risk of severe hypokalemia-associated paresis. Close monitoring of serum K levels should be considered for these patients. Because severe hypokalemia often occurs within hours of methylprednisolone administration, an overnight hospital stay might also be considered.[9,13] It is unclear whether pre-emptive K supplementation should be prescribed to prevent TPP following the use of high-dose corticosteroids. Data supporting K supplementation in the absence of deficiency are currently unavailable. Although the pre-emptive K supplementation was given only from the second dose of methylprednisolone, at which point T4 levels had greatly declined, we observed maintenance of normal serum K levels in a patient predisposed to TPP in whom T4 levels were still elevated. Therefore, we propose that for this particular case, pre-emptive KCl supplementation and close serum K monitoring might have been beneficial to the patient from the first use of high-dose IV corticosteroid, given his thyrotoxic state. Furthermore, some patients may require high-dose methylprednisolone for other medical conditions or less severe ophthalmopathy. If so, postponing methylprednisolone until normal T4 levels are achieved might be considered if the ophthalmic condition allows it.

CONCLUSION

We have reported a case of TPP in which pre-emptive K supplementation was effective in preventing hypokalemia caused by high-dose methylprednisolone administered for

ophthalmopathy associated with uncontrolled Graves disease. In light of the existing literature and the case reported here, we conclude that pre-emptive K supplementation and close serum K monitoring could be beneficial following the administration of high-dose corticosteroids in patients presenting in a thyrotoxic state. Moreover, delaying corticosteroid use until T4 levels have normalized could be considered if the clinical situation allows.

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Amisulpride Augmentation of Clozapine in Clozapine-Resistant Schizophrenia: A Case Series

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INTRODUCTION

It has been estimated that 25% to 30% of individuals with a diagnosis of schizophrenia meet the criteria for treatment-resistant schizophrenia.[1,2] This condition is commonly defined as the persistence of positive and negative symptoms despite 2 or more trials, of adequate dose and duration, of antipsychotic medication, with documented adherence.[2] Currently, the only antipsychotic approved for use in treatment-resistant schizophrenia is clozapine. Of patients with this diagnosis, 30% to 60% will respond to an adequate trial of clozapine, defined as 12 weeks or more of treatment with plasma concentration of at least 1070 nmol/L (350 ng/mL).[2] The remaining 40% to 70% of patients are considered to have clozapine resistance, and augmentation with electroconvulsive therapy (ECT) or other medications is often considered.[3,4] Currently, the Canadian and US schizophrenia guidelines do not provide detailed guidance on augmentation strategies.[1,5] However, an international expert working group recently achieved consensus on the use of amisulpride as an augmentation strategy in clozapine resistance for mixed positive and negative symptoms.[6]

Overall, previous prospective controlled studies have shown mixed results for amisulpride augmentation of clozapine, with both positive and negative findings.[7-9] However, in clinical settings globally and in Canada, amisulpride is sometimes considered, given that its mechanism of action and receptor profile may be complementary to those of clozapine.

Amisulpride is a substituted benzamide antipsychotic with a selective affinity for the dopamine D2 and D3 receptors.[10] At lower doses (50–300 mg/day), amisulpride enhances dopamine transmission by selectively antagonizing presynaptic autoreceptors, contributing to the drug's efficacy in addressing primarily negative symptoms, whereas at higher doses (400–800 mg/day), amisulpride antagonizes postsynaptic D2 and D3 receptors in the limbic system, which is predictive of potent antipsychotic activity.[10-12] Furthermore, amisulpride acts as a potent antagonist at the serotonin 5HT7 receptor, which is postulated to contribute to its antidepressant efficacy.[13,14] The limbic selectivity of amisulpride is associated with a low propensity for causing extrapyramidal side effects.[10] Amisulpride has little or no affinity for D1, D4, D5, serotonin, μ-adrenergic, H1 histaminergic, or anticholinergic receptors.[15] Consequently, it is less likely than some other antipsychotics to increase the burden of side effects characteristic of clozapine, such as sedation, weight gain, and anticholinergic effects.[15] Although amisulpride is not currently marketed or approved for use in clinical practice in North America, in Canada it can be obtained through Health Canada's special access program for drugs.[16]

In this retrospective case series, we describe the practice of amisulpride augmentation of clozapine in a Canadian inpatient setting for treatment-resistant schizophrenia.

METHODS

This retrospective case series involved patients admitted to a provincial tertiary inpatient program that provides specialized treatment and services to patients with treatment-resistant schizophrenia in a multidisciplinary setting, with an average length of stay of 25 weeks. At the study institution, patients' symptom severity is measured by applying the Positive and Negative Syndrome Scale (PANSS) on admission and at discharge. The PANSS is a validated psychiatric rating scale and is considered the gold standard for quantifying symptoms related to schizophrenia in clinical trials. It is also used in clinical practice for monitoring treatment outcomes.[17] At both admission and discharge, the PANSS is administered by the most responsible psychiatrist. Most admitted patients who meet the criteria for clozapine resistance are offered ECT; if this therapy is declined, patient-specific pharmacological strategies are typically offered. The criteria for clozapine resistance are 12 weeks of clozapine therapy at a therapeutic level (measured at least once and preferably twice over the course of treatment) with persistence of positive symptoms according to the PANSS, with 1 item rated at 6 or 2 items rated at 4.

Two of the authors (S.P. and M.S.) conducted a chart review, using electronic records, to identify patients with

clozapine-resistant schizophrenia who underwent amisulpride augmentation of clozapine over the period January 1, 2017, to May 31, 2020. The starting date was chosen because our program did not access amisulpride (through the Health Canada special access program for drugs) before 2017. Of the 6 cases identified through this search, S.P. abstracted data for the first 3 cases, and M.S. abstracted data for the last 3 cases. The information collected for each case was reviewed independently by R.R.

This retrospective case series was approved by the Clinical Research Ethics Boards of the University of British Columbia and Vancouver Coastal Health Authority and employed principles highlighted in the Declaration of Helsinki. Given the retrospective nature of this study, patient consent was waived as per the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and guidance from the local institutional review board.

CASE DESCRIPTIONS

The 6 cases in which patients with clozapine resistance received amisulpride augmentation of their clozapine therapy are summarized in Table 1. All 6 patients were Caucasian. ECT was offered to all of the patients before initiation of amisulpride, and all declined. The mean clozapine dose at the time of admission was 383.3 mg/day, and the mean serum level of clozapine/norclozapine concentration was 1726/1088 nmol/L before initiation of amisulpride. Although the PANSS rating was obtained at the time of admission, rather than the time when amisulpride was started, the psychiatrists' progress notes indicated no marked improvement in clinical presentation from the time of admission to the initiation of amisulpride.

Four of the 5 patients who tolerated amisulpride had a greater than 20% reduction in total PANSS score at the time of discharge (Table 1). In terms of the negative symptoms subscale, 3 of the 5 patients who tolerated amisulpride had a greater than 20% reduction in this symptom domain, despite a higher dosage range of amisulpride. In case 6, amisulpride was discontinued because of symptomatic hyperprolactinemia (amenorrhea); cases 1 to 5 displayed asymptomatic hyperprolactinemia at the time of discharge. Prolactin increases were noted as early as 1 to 2 weeks after starting the amisulpride treatment.

In case 4, the patient's clozapine therapy was discontinued 7 days before discharge as a precautionary measure, because of abnormal ventricular septal motion detected by echocardiography. The patient was maintained on amisulpride monotherapy until discharge.

In case 2, the patient's clozapine dose was decreased because of initiation of fluvoxamine 25 mg/day. Fluvoxamine is a potent inhibitor of cytochrome P450 1A2 (CYP1A2), which is the main enzyme involved in clozapine metabolism.[19] Addition of fluvoxamine to clozapine will result in phenoconversion to poor metabolizer status at CYP1A2.[19] In this patient, fluvoxamine was initiated after assessment of the clozapine–norclozapine ratio by the treating psychiatrist, which indicated extensive metabolizer status at CYP1A2. The serum levels from admission to discharge depicted a change in this ratio from 0.99 to 2.7.

Extrapyramidal symptoms (EPS) associated with the augmentation strategy were recorded if there was any use of anti-EPS medication after initiation of amisulpride or verified symptoms were clearly documented in the patient's chart (or both). No significant changes in EPS were noted in any of the cases, nor was there a significant weight increase for any patient. There was a clinically insignificant increase in QTc interval after initiation of amisulpride in cases 1 and 3 (16 ms and 25 ms from baseline, respectively). Similarly, there was a decrease in QTc interval after initiation of amisulpride in cases 2 and 5 (15 ms and 7 ms from baseline, respectively). The remaining 2 patients did not undergo electrocardiography at a time close to discharge.

DISCUSSION

This case series supports the notion that augmentation of clozapine with amisulpride in patients with clozapine resistance may result in measurable improvements in both positive and negative symptom domains. Multiple confounding factors can influence a reduction in PANSS score in a specialized inpatient setting; consequently, we cannot attribute observed improvements exclusively to amisulpride augmentation. These variables include (but are not limited to) increased contact time with the health care team in a controlled environment and increased availability of cognitive behavioural therapy. Consequently, our data might not be generalizable to outpatient settings. Furthermore, in case 2, augmentation with fluvoxamine occurred concomitantly with amisulpride, which might have contributed to the measurable improvements at the time of discharge.

Although for each patient both admission and discharge PANSS scores were determined by the same psychiatrist, not a masked rater, we could not ensure retrospectively whether the scoring and calculations had been conducted without error or whether observer bias had been avoided. In addition, because the initial PANSS scores were obtained at the time of admission, not at the time of amisulpride initiation, we had to use progress notes to determine if there were marked improvements in the clinical presentation. Consequently, we do not know whether the PANSS scores had already declined, before initiation of amisulpride. Furthermore, given the retrospective nature of this study, data collection was limited to information that was available in the chart.

We strengthened the chart review process by utilizing data abstractors who were clinical pharmacists with specialization in mental health and strong familiarity with the organization of the electronic chart system. Abstracted data

TABLE 1. Summary of Cases[a]

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)[b]	63	31	26	25	59	45
Sex	Male	Male	Female	Male	Male	Female
Length of stay (days)	210	145	123	91	133	139
Clozapine dosage on admission (mg/day)	575	425	250	300	450	300
Clozapine/norclozapine plasma concentration on admission (nmol/L)	2132/1136	1303/1319	1350/639	1443/977	2649/1698	1479/759
Other psychotropic medications on admission	Aripiprazole 400 mg IM q4weeks	Paliperidone LAI 525 mg IM q90days	None	Lithium 600 mg PO qHS	None	None
Clozapine augmentation[c] attempted before admission	Olanzapine, loxapine, aripiprazole	Paliperidone, olanzapine	None	None	Aripiprazole	None
Duration of clozapine use before amisulpride (days)	6804	188	264	352	10 573	2369
Clozapine dose at discharge (mg/day)	500	125	225	Discontinued	400	300
Clozapine/norclozapine plasma concentration at discharge (nmol/L)	1244/663	2284/848	1891/827	NA	2177/1342	1640/817
Amisulpride dose at discharge	200 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID	None
Other psychotropics at discharge	None	Fluvoxamine 25 mg daily	None	Quetiapine 50 mg PO hs	None	Brexpiprazole 2 mg PO daily
Amisulpride duration (days)	61	53	90	84	60	60
PANSS total score						
On admission	102	118	84	79	94	78
At discharge	80	90	67	47	83	78
Change[d]	–30.6%	–31.8%	–31.5%	–34.7%	–17.2%	0%
PANSS positive subscale score						
On admission	23	35	20	26	25	19
At discharge	17	25	18	12	20	21
Change[d]	–37.5%	–35.7%	–15.4%	–73.7%	–27.8%	+16.7%
PANSS negative subscale score						
On admission	25	21	18	19	23	23
At discharge	21	19	18	10	18	18
Change[d]	–22.2%	–14.3%	0%	–75%	–31.3%	–31.3%
QTc (ms)						
On admission	458	439	416	422	469	460
At discharge	474	424	441	NA	462	NA
Prolactin (µg/L)						
On admission	NA	20.7	8.9	11.4	21.7	NA
After starting amisulpride (no. of days)	106 (7 days)	39.9 (10 days) 45.7 (24 days)	133.4 (12 days)	91.1 (38 days)	65.5 (14 days)	215.6 (18 days) 197 (55 days) 16.0 (26 days post stop)
BMI						
On admission	23.7	37.0	36.1	21.3	23.1	22.3
At discharge	21.1	32.8	34.9	21.4	23.1	21.3
Tobacco smoking status	Smoker	Smoker	Smoker	Smoker	Smoker	Nonsmoker

LAI = long-acting injection, NA = not available, PANSS = positive and negative syndrome scale.
[a]All patients had a diagnosis of treatment-resistant schizophrenia.
[b]Age is presented in years at the time of admission.
[c]Clozapine augmentation before admission represents antipsychotics tried in the past to augment clozapine therapy.
[d]Obermeier and others[18] have provided information about calculation and interpretation of PANSS scores.

for each case were also reviewed independently by another clinical pharmacist.

Hyperprolactinemia was a consistent finding across all 6 patients. In a 2-week study of patients with schizophrenia, prolactin elevation was markedly greater with amisulpride than with other atypical agents.[20] Elevated prolactin levels have been associated with oligomenorrhea, amenorrhea, galactorrhea, decreased libido, infertility, breast cancer in women,[21] and decreased bone mass; these outcomes should be taken into account when augmentation is being considered.[22] Although amisulpride has been associated with dose-dependent QT prolongation,[23] the patients described in our case series did not experience clinically relevant increases in QT at therapeutic doses of amisulpride.

As mentioned above, amisulpride is not readily available in Canada and requires approval from Health Canada. Such approval generally takes about 24 hours, and shipping to the practitioner's office or pharmacy takes another 6 to 8 weeks. Consequently, advance planning is important. Amisulpride also poses cost concerns, as it is available from only 1 manufacturer, and a single amisulpride 400-mg tablet costs twice as much as a clozapine 200-mg tablet. A cost–utility analysis would be of benefit to evaluate the overall cost effectiveness of this intervention.

CONCLUSION

To our knowledge, this is the first study examining the practice of augmentation of clozapine therapy with amisulpride in Canada, based on obtaining the medication through Health Canada's special access program for drugs. Given the extended duration of stay in our tertiary facility, we have been able to provide details about the tolerability and efficacy of this augmentation strategy for the cases reported here. In light of mixed evidence of benefit, elevated costs, and barriers to access, the decision to prescribe amisulpride in Canada should be taken with caution and proactive planning. Further studies are needed to better understand the long-term efficacy and tolerability of this augmentation strategy. Future studies should focus on better characterization of subgroups of patients with treatment-resistant schizophrenia, to allow for greater precision in the selection of patients most likely to benefit from such an augmentation strategy.

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Role of Free Valproic Acid Levels in a Patient with Severe Hypoalbuminemia: A Case Report

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INTRODUCTION

Valproic acid (VPA) is an antiepileptic drug used for the treatment of various seizure types, psychiatric disorders, and migraines.[1] It has a complex mechanism of action, most likely associated with potentiating the effect of γ-aminobutyric acid (GABA) in the central nervous system and thus inhibiting neuronal excitation.[2,3] VPA has good oral bioavailability, is widely distributed in the body, and is highly protein bound (up to 90%), mainly to albumin.[4,5] It is metabolized in the liver primarily through glucuronidation and β-oxidation and should be used cautiously in those at risk of liver dysfunction.[6]

Given its narrow reference range, wide intra- and inter-patient variability, and diverse toxicity profile, VPA is a prime candidate for therapeutic drug monitoring. Current therapeutic drug monitoring practices involve measuring total VPA levels in the serum, even though it is the free drug that exhibits pharmacologic effect. Because of its high protein binding, conditions that result in an acute decrease in albumin would thus shift the equilibrium to a higher free fraction of VPA, resulting in more drug being available to elicit effect and increasing the risk of toxicity. Furthermore, VPA toxicity has a range of presentations, making its clinical diagnosis challenging.[7-9]

This case report describes a unique presentation of VPA toxicity and emphasizes the importance of determining free VPA levels, especially in the setting of hypoalbuminemia.

CASE REPORT

A patient in their late 40s was admitted to hospital from a long-term care facility with severe agitation and hypotension.* The patient had vague abdominal pain, decreased oral intake, and weight loss of about 4.5 kg over the course of a month. Two years before the current presentation, the patient had experienced a left middle cerebral artery ischemic stroke, which caused significant cognitive deficits and right-side hemiparesis. Shortly after the stroke, the patient had a first episode of an isolated tonic-clonic seizure, and VPA 500 mg orally, twice a day, was initiated. During the year preceding admission to hospital, the patient had been maintained on the same dose, with documentation of therapeutic total VPA level and normal albumin, and there was no documented recurrence of seizure activity or adverse effects.

The patient's past medical history was pertinent for celiac disease, thrombocytosis (baseline platelet count 500 to 700 × 10^9/L), type 2 diabetes mellitus, and recurrent episodes of aspiration pneumonia; one of these episodes led to a hospital admission 3 months before the current presentation. The regimen of medications before admission was stable, with no drug–drug interactions noted. In addition to VPA, the pre-existing home medications were atorvastatin, apixaban, topiramate, gabapentin, pantoprazole, calcium, and vitamins.

On admission, the patient had an albumin level of 10 g/L (reference range 34–54 g/L), profound hypotension, and lactate of 4.7 mmol/L (reference range 0.5–1 mmol/L). Fluid resuscitation was accomplished with 7 L of IV crystalloids; in addition, 25% albumin was given by the IV route every 6 hours for 24 hours, and norepinephrine and vasopressin were initiated. Piperacillin–tazobactam, vancomycin, and hydrocortisone were initiated empirically for possible septic shock, and the patient was transferred to the intensive care unit (ICU) for ongoing management.

The results of laboratory tests at the time of admission showed the following coagulation abnormalities: platelet count 185 × 10^9/L (reference range 150–400 × 10^9/L) and fibrinogen 0.7 g/L (reference range 2.0–4.0 g/L). Several electrolyte derangements were also noted: potassium 3.1 mmol/L (reference range 3.5–5.1 mmol/L), sodium 125 mmol/L (reference range 135–145 mmol/L), magnesium 0.59 mmol/L (reference range 0.75–1.2 mmol/L), phosphate 0.67 mmol/L (reference range 0.8–1.45 mmol/L), and ionized calcium 0.97 mmol/L (reference range 1.13–1.4 mmol/L). The electrolyte abnormalities were believed to reflect poor nutritional status. Measurement of total VPA serum trough concentration was ordered to rule out acute VPA toxicity; the level was

*The authors were unable to obtain patient consent. Therefore, potentially identifiable information not relevant to the case has been omitted from the manuscript.

slightly subtherapeutic, at 341 µmol/L (reference range 350–850 µmol/L), and VPA was therefore continued.

Cultures of blood, sputum, and urine samples obtained on admission did not grow any pathogens. Computed tomography (CT) of the head, to rule out structural causes of agitation, showed no acute abnormalities. CT of the abdomen and pelvis was also done to investigate potential organic causes of abdominal pain; this imaging revealed diffusely increased subcutaneous fat throughout the torso and thighs suggestive of anasarca, multifocal and extensive thickening of the colon suggesting colitis, and mild sigmoid diverticulosis. At this point, a gastroenterology consultation was requested.

Testing for tissue transglutaminase immunoglobulin A yielded a positive result, and it was noted (following confirmation with the long-term care facility) that the patient had not been receiving a gluten-free diet since the most recent discharge from hospital about 3 months beforehand. A protein-losing enteropathy was diagnosed, which explained the severely low albumin and associated anasarca. Throughout the admission, coagulation markers continued to decline, with fibrinogen and platelet nadirs of 0.5 g/L and 95 × 10^9/L, respectively. A hematology opinion was requested, and hemolysis was ruled out.

On day 3 of the ICU admission, measurement of serum ammonia level was requested, and a send-out test for free VPA level was arranged. These tests showed elevation of both ammonia and free VPA (274 µmol/L; reference range 17–76 µmol/L). At this time, the VPA was discontinued and levetiracetam 500 mg orally, twice daily, was started. Approximately 1 week after discontinuation of VPA, the patient's fibrinogen and platelet counts began to recover (Figure 1), and the agitation resolved.

DISCUSSION

VPA has complex pharmacokinetics, including a low hepatic extraction ratio and nonlinear profile due to saturable protein binding.[1] When the dose of VPA is increased, the change in total serum concentration is not proportional to the change in dose. Rather, the change in total serum concentration is less than might be expected with a dose increase, whereas the change in free VPA is much greater than expected, because albumin binding sites are already occupied. Therefore, in situations involving alterations in albumin, there can be a substantial effect on the free fraction of VPA, disproportionate with total concentration.

Akin to its pharmacological effect, unbound VPA causes toxic effects, and the incidence and severity of these adverse effects depends on the concentration. The clinical presentation of toxicity is variable and can affect many body systems, making it challenging to predict what will occur. Commonly observed adverse effects include nausea, dyspepsia, tremor, and visual disturbances. In rare circumstances, patients may experience neurotoxicity, which manifests as myoclonus, miosis, severe agitation, or seizures, and hematological toxicities, including hypofibrinogenemia and thrombocytopenia. In cases of severe toxicity or overdose, anion gap metabolic acidosis, respiratory depression, hypotension, acute respiratory distress syndrome, and cerebral edema may also occur.[7-11]

Significant elevation of free VPA in patients with hypoalbuminemia has been highlighted previously in several case reports and observational studies.[12-15] However, little has been reported concerning critically ill patients. Elevated free VPA in critically ill patients has been reported in 4 case reports and a case series of 15 patients (median percentage of free VPA 48%, interquartile range 15%–89%).[16-20] However, not all patients exhibited probable VPA toxicity. Reported adverse drug events that were possibly related to VPA were hyperammonemia, elevation of liver enzymes, thrombocytopenia, and lethargy.[16-20]

To our knowledge, the case reported here is the first to describe diverse presentation of VPA toxicity secondary to the elevated free fraction (hematological abnormalities combined with agitation) in a critically ill patient. In addition, this case highlights the prompt reversal of such adverse effects upon discontinuation of VPA. In this case, the patient had thrombocytosis at baseline and presented with a remarkable drop in platelet count. Additionally, the patient's fibrinogen levels were low at the time of admission and continued to decline over the first few days of the hospital stay. Upon discontinuation of VPA, both platelet count and fibrinogen level began to recover.

A modest amount of literature suggests that VPA can affect fibrinogen, including a case report of intracranial hemorrhage secondary to VPA-induced hypofibrinogenemia.[21,22] The mechanism of this effect has not been well documented, and recovery is generally quick (within 5 days of VPA discontinuation).[21] In our case, other differential diagnoses for the patient's hematological abnormalities were

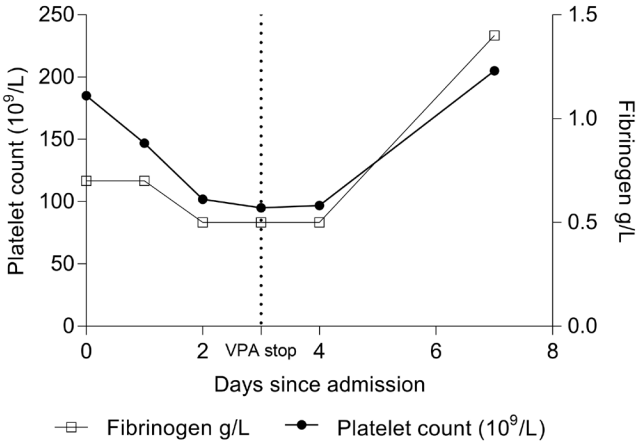

FIGURE 1. Platelet count and fibrinogen levels throughout the first week of hospital admission. The dotted line reflects the day when valproic acid (VPA) was discontinued.

excluded by our hematology colleagues. This patient also presented with severe agitation, which is an unusual manifestation of VPA toxicity. Given the proposed action of VPA on GABA receptors, we would typically expect patients with VPA toxicity to present with depressed mental status. However, some previous literature suggests that VPA neurotoxicity can present as agitation and in some instances can also lead to further seizures.[10,23] Ultimately, this patient's laboratory abnormalities and clinical symptoms began to normalize after discontinuation of VPA. On the basis of the patient's presentation and recovery, we calculated the Naranjo score to help determine the likelihood that the symptoms were a result of VPA.[24] The Naranjo score was 6, suggesting that the presenting abnormalities were "probably" due to VPA. No other medication changes were made at the same time as the VPA discontinuation, aside from hydrocortisone discontinuation, which was less likely than VPA to have contributed to the current finding.

Current practice for therapeutic drug monitoring of VPA is to measure total trough concentrations, because of the limited availability and greater cost of measuring free levels (although the cost varies from one centre to another). In this case, testing of free VPA was not available in any of the local centres, and the sample was therefore sent outside the province for analysis, which led to additional shipping costs. Unfortunately, no equations are available that allow accurate calculation of free VPA concentration from total serum concentration, and the greatest discordance appears to occur in critically ill patients.[25,26]

This case highlights that total VPA concentration can be misleading in patients with hypoalbuminemia, and it emphasizes the importance of monitoring free, or unbound, VPA concentration. Because albumin is a negative acute-phase reactant, patients who are acutely ill and receiving VPA are at the highest risk of experiencing toxic effects, and VPA should therefore be used with caution and concentrations should be monitored carefully. Patients with low albumin levels often have various other comorbidities (including chronic kidney disease, older age, acute illness, and malnourishment) that put them at greater risk of adverse drug reactions; measuring only the total VPA serum concentration in these patients may be misleading.

This report is limited by the inherent nature of case reports. The description of a single patient case limits the generalizability of the findings. In addition, there is a risk of bias secondary to overinterpretation of the patient's clinical progress. Nonetheless, this case serves to emphasize that clinicians must be vigilant in monitoring free VPA in critically ill patients with hypoalbuminemia.

CONCLUSION

VPA toxicity can present in many ways, and it can therefore be challenging to diagnose clinically. Total VPA levels may underestimate the true drug exposure in patients with hypoalbuminemia and can potentially result in failure to recognize toxicity. Measuring free VPA levels in patients with hypoalbuminemia, particularly in settings of acute changes in albumin, is a better predictor of VPA exposure.

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Advocacy: CSHP's Renewed Vision for Hospital Pharmacy Excellence

Jody Ciufo

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Advocacy is an integral component of your professional association—that's what Canadian Society of Hospital Pharmacists (CSHP) members tell us each year in our national membership surveys. Members say that advocacy is one of the top-three core values they associate with CSHP, and in 2021, 99% of our survey respondents indicated that "advising government on legislation and public policy" was an essential or acceptable role for CSHP. Eighty-nine per cent of 2021 respondents felt that it was essential for CSHP to act as the voice of hospital pharmacy in Canada.

As CSHP's CEO, I hear you loud and clear. CSHP has always engaged in advocacy, and we're proud to have built close working relationships with government agencies and stakeholders across the country. That said, in our 2020–2023 Strategic Plan, CSHP focused on achieving sustainability as an organization; we strengthened our foundation by modernizing information systems, enhancing our financial sustainability, and investing in human resources. Now, as we prepare to transition into a new strategic planning phase in 2023 and beyond, you'll see CSHP focus more attention on hospital pharmacy advocacy. Our goal is to make CSHP the most effective voice for our profession, leveraging thoughtful strategy and solid evidence to achieve meaningful change.

"Advocacy" is a term we hear frequently, but what does effective advocacy really require? Often, we associate advocacy with raising public awareness about the value of hospital pharmacy teams, perhaps through initiatives like Pharmacy Appreciation Month. Public education and recognition for what we do is important. More critical is advocacy targeted directly at laws, regulations, policies, and funding so that we can bring about systemic change. We have expertise and evidence that will have a great and lasting impact on patient care across the country.

As the national voice of hospital pharmacy, CSHP aims to provide clear, focused communication with Canadian legislators, regulators, and policy-makers. We will continue to work closely with Health Canada and expand our reach to other departments and agencies across all levels of government. This way, hospital pharmacy expertise can shape policy from its very germination, to create optimal outcomes for our patients and to support excellence in the profession. Effective advocacy also means articulating the value of hospital pharmacy to decision makers when it comes to funding opportunities, so that the knowledge and innovation of hospital pharmacy teams can shine to their greatest potential. In these efforts, we aim to identify clear and precise objectives, to support evidence-based positions, and to highlight issues in which hospital pharmacy teams offer unique expertise.

As we prepare for our next strategic plan, I look forward to working alongside you to achieve meaningful, lasting change in our health systems. Our vision for CSHP's legacy and impact is ambitious, but we are uniquely positioned as a united profession to enhance the use of safe, effective medication in Canada. Together, we can make real change.

Jody Ciufo, MBA, is Chief Executive Officer of the Canadian Society of Hospital Pharmacists.

Défense des intérêts : Renouvellement de la vision de la SCPH concernant l'excellence en pharmacie hospitalière

par Jody Ciufo

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La défense des intérêts fait partie intégrante de votre association professionnelle – c'est ce que nous disent chaque année les membres de la Société canadienne des pharmaciens d'hôpitaux (SCPH) dans les sondages nationaux. Ils estiment que la défense des intérêts est l'une des trois principales valeurs fondamentales qu'ils associent à la SCPH, et en 2021, 99 % des répondants à notre sondage ont indiqué qu'un des rôles essentiels ou acceptables de la SCPH était de « conseiller le gouvernement sur la législation et les politiques publiques ». Quatre-vingt-neuf pour cent des répondants de 2021 estiment qu'il est essentiel que la SCPH représente la voix de la pharmacie hospitalière au Canada.

En tant que directrice générale de la SCPH, je vous entends haut et fort. La SCPH s'est toujours engagée dans la défense des intérêts et nous sommes fiers d'avoir établi des relations professionnelles étroites avec les organismes gouvernementaux et les intervenants partout au pays. Cela dit, dans son Plan stratégique 2020-2023, la SCPH s'est concentrée sur la durabilité en tant qu'organisation. Nous avons renforcé nos assises en modernisant les systèmes d'information, en améliorant notre viabilité financière et en investissant dans les ressources humaines. Maintenant, tandis que nous nous préparons à entamer une nouvelle phase de la planification stratégique en 2023 et au-delà, vous constaterez que la SCPH porte une plus grande attention à la défense de la pharmacie hospitalière. Notre objectif est que la voix de la SCPH soit la plus efficace de la profession en sachant tirer parti d'une stratégie réfléchie et d'éléments probants solides pour la réalisation de changements significatifs.

« Défense des intérêts » est une expression que nous entendons fréquemment, mais que requiert vraiment une défense efficace des intérêts? Souvent, nous l'associons à la sensibilisation du public à la valeur des équipes de pharmacie hospitalière, peut-être grâce à des initiatives comme le Mois de la reconnaissance de la pharmacie. L'éducation du public et la reconnaissance de ce que nous faisons sont importantes. La défense des intérêts qui cible directement les lois, les règlements, les politiques et le financement est plus cruciale pour apporter un changement systémique. Notre expertise et les preuves dont nous disposons auront un impact important et durable sur les soins des patients partout au pays.

En tant que porte-parole nationale de la pharmacie hospitalière, la SCPH cherche à assurer une communication claire et ciblée avec les législateurs, les organismes de réglementation et les décideurs canadiens. Nous continuerons de travailler étroitement avec Santé Canada et d'étendre notre portée à d'autres ministères et organismes, et cela à tous les niveaux de gouvernement. De cette façon, l'expertise de la pharmacie hospitalière pourra façonner la politique dès sa germination, afin d'obtenir des résultats optimaux pour nos patients et de soutenir l'excellence dans la profession. Une défense efficace des intérêts signifie également qu'on insiste sur la valeur de la pharmacie hospitalière auprès des décideurs lorsqu'il s'agit d'occasions de financement, afin que les connaissances et l'innovation des équipes de pharmacie hospitalière puissent atteindre leur plein potentiel. Grâce à ces efforts, nous cherchons à définir des objectifs clairs et précis, à soutenir des positions fondées sur des données probantes et à mettre en évidence des problèmes qui pourraient bénéficier de l'expertise unique des équipes de pharmacie hospitalière.

Alors que nous préparons notre prochain plan stratégique, j'ai hâte de travailler à vos côtés pour apporter des changements significatifs et durables à nos systèmes de santé. Notre vision de la portée et de l'impact de la SCPH est ambitieuse, mais nous occupons une position unique en tant que membres unis d'une profession pour encourager l'utilisation de médicaments sûrs et efficaces au Canada. Ensemble, nous pouvons faire bouger les choses.

Jody Ciufo, M.B.A., est directrice générale de la Société canadienne des pharmaciens d'hôpitaux.