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Pages 1–88

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Mount Wintour
Kananaskis Country, Alberta

In this issue / Dans ce numéro :

- Pharmacist-Led DOAC Monitoring Clinic
- Medication Errors and Timing of Pharmacy-Led BPMH in Parkinson Disease
- Antimicrobial Use in a Pediatric Population
- Medication Reconciliation by Resident Physicians for Children with Asthma
- Conflict between Pharmacy Preceptors and Pharmacy Learners
- Identification of Staphylococci by PCR Directly from Positive Blood Culture
- Factors Associated with Prescribing of IV Iron
- Stability of Generic Formulations of Bortezomib
- BUD Guidelines for Single-Use Vials
- Pénuries de médicaments au Canada
- SC Pamidronate for Hypercalcemia in Hospice Setting
- Microdosing for Transition from Methadone to Buprenorphine

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EDITORIAL / ÉDITORIAL

Evidence-Based Medicine in the COVID-19 Era 3
Cynthia A Jackevicius

Une médecine fondée sur les données probantes à l'époque de la COVID-19 5
Cynthia A. Jackevicius

ORIGINAL RESEARCH / RECHERCHE ORIGINALE

Assessment of a Pharmacist-Led Direct Oral Anticoagulant Monitoring Clinic. 7
Jenna Haché, Kwadwo Osei Bonsu, Rufaro Chitsike, Hai Nguyen, and Stephanie Young

Correlation between Medication Administration–Related Errors in Patients with Parkinson Disease and Timing of Pharmacy-Led Best Possible Medication Histories 15
Emily Cowley, Michael R Miller, Charles Yin, and Lynne Kelly

Profile of Antimicrobial Use in the Pediatric Population of a University Hospital Centre, 2015/16 to 2018/19 21
Lydia R Rahem, Bénédicte Franck, Hélène Roy, Denis Lebel, Philippe Ovetchkine, and Jean-François Bussières

Completeness of Medication Reconciliation Performed by Pediatric Resident Physicians at Hospital Admission for Asthma. 30
Ashley Martin, Jaime McDonald, and Joanna Holland

Conflict between Pharmacy Preceptors and Pharmacy Learners in Experiential Education 36
Jennifer Kendrick, Arielle Beauchesne, Yunji Valerie Lee, Sue Corrigan, and Roxane Carr

Identification of Staphylococci by Polymerase Chain Reaction Directly from a Positive Blood Culture and Effect on Patient Care 43
Molly Wade-Cummings, Jonathan F Mailman, Michelle L Degelman, Casey Phillips, and Jason R Vanstone

Patient Factors Associated with Prescribing of Iron for IV Administration: A Descriptive Study. 50
Thomas Brownlee, Deonne Dersch-Mills, Ginny Cummings, Tanya Fischer, Rhonda Shkrobot, Jeremy Slobodan, and Jenny Wichart

Stability of Generic Formulations of Bortezomib 1.0 and 2.5 mg/mL in Vials and Syringes Stored at 4°C and Room Temperature (23°C or 25°C) 57
Shirley Law, Flay Charbonneau, John Iazzetta, William Perks, Nathan H Ma, and Scott E Walker

INNOVATIONS IN PHARMACY PRACTICE / INNOVATIONS EN PRATIQUE PHARMACEUTIQUE

Implementation of Beyond-Use Date Guidelines for Single-Use Vials at a Pediatric Hospital 70
Kathryn Hollis, Florence Payen, and Régis Vaillancourt

Pénuries de médicaments au Canada au cours des 24 derniers mois : la situation ne fait que s'empirer 75
Marine Floutier, Suzanne Atkinson, Denis Lebel et Jean-François Bussières

CASE REPORT / OBSERVATION CLINIQUE

Subcutaneous Infusion of Pamidronate in a Hospice Patient with Hypercalcemia: A Case Report 80
Chris Vandevelde and Jordan Ho

Successful Transition from High-Dose Methadone to Buprenorphine via Microdosing in the Outpatient Setting: A Case Report. 83
Siavash Jafari and Reza Rafizadeh

COMMENTARY FROM THE PRESIDENTIAL TEAM / COMMENTAIRE DE L'ÉQUIPE PRÉSIDENTIELLE

Quelques mots sur mon association 87
Zack Dumont

Talkin' 'bout My Association 88
Zack Dumont

On the Front Cover / En page couverture. 4

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Evidence-Based Medicine in the COVID-19 Era

Cynthia A Jackevicius

Evidence-based medicine (EBM) is created at the intersection of the best available clinical evidence, clinician expertise, and patient values.[1] During the COVID-19 pandemic, we have been short on high-quality evidence because of a lack of clinical trials and a sparsity of clinician expertise, given limited experience with the unknown entity of COVID-19. Absence of an evidence foundation, coupled with a rapidly changing evidence base, has created great uncertainty, sometimes leading to emotion-based, rather than evidence-based, decision-making.

At the start of the COVID-19 pandemic, clinical decisions relied on indirect evidence (e.g., from animal studies or the H1N1 experience a decade ago) and the few available case reports/series from China, where COVID-19 first emerged. The evidence base subsequently expanded to include observational studies from the next "hot spots", Seattle (Washington) and Italy. Later still, evidence overload arose, as the floodgates opened with the appearance of an enormous volume of observational studies, including many in non-peer-reviewed "preprint servers" (e.g., www.medRxiv.org). Finally, some randomized controlled trials were completed worldwide at breakneck speed. Although this evidence progression may be an uncomfortable experience for clinicians and the general public alike, it is precisely how EBM works, with an actively evolving evidence base, subsequently higher-quality evidence, and greater certainty over time.

This acceleration of evidence generation has challenged our ability to keep up and has magnified the cracks in our current methods of evidence synthesis. If COVID-19 has taught us anything, it is the importance of evidence and EBM skills in our clinical decision-making. With new evidence emerging daily, COVID-19 has highlighted the value of lifelong learning, of not remaining stagnant in our knowledge. Never before has it been more obvious that we need to stay abreast of new evidence and appraise it objectively to be able to make optimal, evidence-informed, individualized decisions with patients. The high uncertainty of the evidence has also underscored the importance of incorporating patient values and preferences in balancing the potential risks and benefits of therapies, albeit in an environment of amplified tensions between societal and individual values.

The tidal wave of COVID-19 evidence has accelerated the pressure for innovation and creativity in EBM. In areas where we might always have wanted further development, COVID-19 has mandated change. While the pandemic has generated public interest in science, rapidly evolving evidence has also created public confusion due to inconsistent messaging. Despite long-standing calls to advance how evidence is synthesized for "evidence consumers", it has become clear that we need a coordinated system to organize rapidly developing and massive evidence bases. Rapid systematic review methods have been further refined, including publicly available initiatives, and "living" systematic reviews and recommendation maps (https://covid19.evidenceprime.ca/), which are updated as new evidence is released, have multiplied.[2-5] Collaborations among clinical trialists to conduct prospective meta-analyses of ongoing clinical trials, synthesizing evidence as it is being created, has been another innovation in evidence synthesis.[6] Finally, artificial intelligence initiatives have attempted to identify and synthesize the evolving evidence.[7] While these new initiatives are motivated by the urgency of understanding COVID-19 evidence, it is hoped that they may also provide an impetus to create higher standards in how all evidence, related to COVID-19 or otherwise, is synthesized and made available to clinicians, including enhanced leadership in evidence stewardship. In this time of uncertainty during the COVID-19 pandemic, the foundation of EBM principles and their revitalized evolution are more important than ever.

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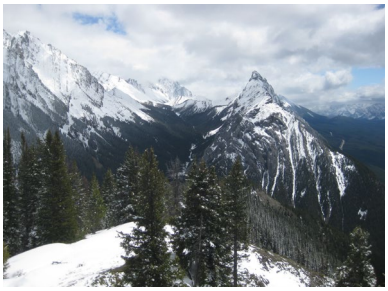

Mount Wintour, Kananaskis Country, Alberta

This photograph showcases the snowy pinnacle of Mount Wintour in Kananaskis Country, Alberta. June Chen took this photo with a Canon PowerShot SD1100 IS digital camera while she was hiking the King Creek Ridge in May 2019. June is a clinical pharmacist with the University of Alberta Hospital in Edmonton. She practises on the cardiac intensive care and cardiovascular surgery units. During the summer months, she enjoys hiking in the mountains, and all year round, she likes to dance contemporary jazz.

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Une médecine fondée sur les données probantes à l'époque de la COVID-19

par Cynthia A. Jackevicius

La médecine basée sur les données probantes se situe à la croisée des meilleures preuves cliniques disponibles, de l'expertise des cliniciens et des valeurs des patients[1]. Pendant la pandémie de COVID-19, nous avons manqué de données probantes de qualité à cause du manque d'essais cliniques et de la rareté de l'expertise des cliniciens, étant donné l'expérience limitée relative à l'entité inconnue de la COVID-19. L'absence d'une base d'éléments probants associée à des données en constante mutation est à l'origine d'une grande incertitude, qui a entraîné parfois des prises de décision fondées sur l'émotion plutôt que sur des éléments probants.

Au début de la pandémie de COVID-19, les décisions cliniques s'appuyaient sur des preuves indirectes (p. ex., sur des études animales ou sur l'expérience du H1N1 d'il y a dix ans) et sur quelques études ou séries de cas disponibles en provenance de Chine, où la COVID-19 est apparue en premier. La base d'éléments probants s'est ensuite élargie pour y inclure des études observationnelles provenant des « points chauds » subséquents : Seattle, Washington et l'Italie. Plus tard, il y a eu une surabondance de preuves à mesure de l'apparition d'une énorme quantité d'études observationnelles, dont beaucoup figuraient dans des « moteurs de prépublication » (p. ex., www.medRxiv.org) sans avoir fait l'objet d'un examen par des pairs. Enfin, des essais contrôlés aléatoires ont été menés partout dans le monde à une vitesse record. Bien que l'établissement de ces preuves puisse être une expérience désagréable pour les cliniciens comme pour le grand public, c'est précisément de cette manière que fonctionne la médecine fondée sur les données probantes : avec une base d'éléments probants en constante évolution, suivie par des preuves de meilleure qualité et une plus grande certitude avec le temps.

Cette accélération de la production de preuves a remis en question notre capacité à garder la cadence et a amplifié les failles de nos méthodes actuelles relatives à la synthèse des preuves. Si la COVID-19 nous a enseigné quelque chose, c'est bien l'importance des données probantes et des compétences en matière de médecine factuelle dans notre processus de prise de décision clinique. Avec les nouvelles données probantes qui émergent chaque jour, la COVID-19 a permis la mise en valeur de l'apprentissage continu et l'importance de ne pas laisser stagner nos connaissances. Jamais auparavant la nécessité de se tenir au courant des nouveaux éléments de preuve et de les évaluer de manière objective n'a été aussi évidente afin que les décisions prises en collaboration avec les patients soient optimales, individualisées et appuyées par des preuves. La grande incertitude relative aux éléments de preuve a également permis de mettre en exergue l'importance d'intégrer les valeurs et les préférences des patients pour équilibrer les risques et les avantages potentiels des thérapies, même dans un environnement marqué par de plus grandes tensions entre les valeurs sociétales et individuelles.

Le raz-de-marée des données probantes liées à la COVID-19 a intensifié la course à l'innovation et la créativité dans le champ de la médecine fondée sur les preuves. La COVID-19 a imposé des changements dans des domaines où on aurait toujours souhaité un développement plus poussé. Alors que la pandémie a généré l'intérêt du public pour la science, l'évolution rapide des éléments de preuve a généré des messages incohérents qui ont semé la confusion chez les gens. Malgré les appels lancés depuis longtemps pour faire avancer la manière dont les preuves sont présentées aux « consommateurs de preuves », il est clair désormais que nous avons besoin d'un système coordonné pour organiser les données de base massives qui connaissent un rapide développement. Un raffinement des méthodes d'examen systématiques et rapides a eu lieu, y compris la prise d'initiatives pour mettre l'information à la portée du public, et les examens systématiques « vivants » et une carthographie des recommandations (https://covid19.evidenceprime.ca/) actualisés à mesure de l'apparition de nouvelles preuves se sont multipliés[2-5]. La collaboration entre les cliniciens spécialistes des essais, qui menaient des méta-analyses prospectives d'essais cliniques en cours, en synthétisant les données probantes au fur et à mesure de leur création sont d'autres innovations apportées à la synthèse des preuves[6]. Enfin, le développement d'initiatives liées à l'intelligence artificielle ont permis de déterminer les preuves en évolution et de les synthétiser[7]. Alors que ces nouvelles initiatives sont motivées

par l'urgence visant à comprendre les éléments probants liés à la COVID-19, il faut espérer qu'elles donneront aussi une impulsion à l'établissement de normes plus élevées quant à la manière de synthétiser l'ensemble des données probantes relatives à la COVID-19 et à toute autre maladie, pour qu'elles soient disponibles aux cliniciens et qu'elles servent également à renforcer le leadership en matière de gestion des données probantes. En ces temps marqués par l'incertitude liée à la pandémie de COVID-19, les principes de base de la médecine fondée sur les données probantes et la revitalisation de leur évolution sont plus importants que jamais.

[Traduction par l'éditeur]

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Assessment of a Pharmacist-Led Direct Oral Anticoagulant Monitoring Clinic

Jenna Haché, Kwadwo Osei Bonsu, Rufaro Chitsike, Hai Nguyen, and Stephanie Young

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) are recommended as first-line therapy for treatment and prevention of venous thromboembolism (VTE) and prevention of stroke related to nonvalvular atrial fibrillation. Recent publications have suggested incorporating DOAC monitoring into anticoagulant management clinics. The Eastern Health Adult Outpatient Thrombosis Service (Newfoundland and Labrador) includes a pharmacist-led DOAC monitoring clinic that uses standardized evidence-based care processes.

Objectives: To describe a new pharmacist-led DOAC monitoring clinic and to assess patients' adherence to medication therapy, adherence to guideline-recommended frequencies for blood work, and adverse and non-adverse events.

Methods: This retrospective chart review involved patients who attended their first visit to the DOAC clinic between October 10, 2017, and May 31, 2018. Patients were followed until November 30, 2018. Data were abstracted from electronic hospital records and the provincial pharmacy network. Descriptive statistics were used to analyze the data: categorical variables were presented as frequencies and percentages; continuous variables were analyzed and presented as means with standard deviations and, where applicable, as medians with interquartile ranges.

Results: Forty-seven patients, who attended a total of 74 clinic visits, were included. Twenty-eight patients (60%) were adherent to their DOAC therapy. All patients had blood work completed before each clinic appointment. The mean time between the first and second sets of blood tests was 6.2 (standard deviation [SD] 1.4) months and between the second and third sets of blood tests was 5.1 (SD 1.0) months. There were no episodes of VTE or major bleeding. There was 1 cerebrovascular accident (3.2 events per 100 person-years, 95% confidence interval [CI] 0.2–15.7) and 5 episodes of clinically relevant non-major bleeding (12.8 events per 100 person-years, 95% CI 4.1–30.1). Pharmacists identified 51 issues at the clinic appointments, of which 48 were medication-related. Referral to the Thrombosis Service physician was required to resolve 8 (16%) of the issues identified. A brief discussion between the Thrombosis Service physician and pharmacist was required to resolve 30 (59%) of the issues, with 13 (25%) resolved by the pharmacist alone.

Conclusions: This study described the implementation and outcomes of a novel pharmacist-led DOAC clinic. Clinic patients underwent blood work at recommended intervals and received guidance on adherence and adverse events; as such, patients had follow-up that aligned with guideline recommendations.

Keywords: anticoagulant, direct oral anticoagulant, drug monitoring

RÉSUMÉ

Contexte : Les anticoagulants oraux directs (AOD) sont recommandés comme thérapie de première ligne pour le traitement et la prévention de la thromboembolie veineuse (TEV) et la prévention des AVC liés à la fibrillation auriculaire non valvulaire. Des publications récentes ont proposé d'incorporer le contrôle des AOD dans les cliniques des anticoagulants. L'Eastern Health Adult Outpatient Thrombosis Service (St John's, Terre-Neuve-et-Labrador) comprend une clinique de surveillance des AOD, dirigée par des pharmaciens qui utilisent des processus de soins standardisés basés sur des éléments de preuve.

Objectifs : Décrire une nouvelle clinique de surveillance des AOD dirigée par des pharmaciens et évaluer l'adhésion des patients à la pharmacothérapie, le respect de la fréquence des analyses sanguines recommandées dans les lignes directrices ainsi que les effets indésirables et ceux qui ne le sont pas.

Méthodes : Cet examen rétrospectif des dossiers impliquait des patients ayant effectué leur première visite à la clinique AOD entre le 10 octobre 2017 et le 31 mai 2018. Les patients étaient suivis jusqu'au 30 novembre 2018. Les données analysées provenaient de dossiers d'hospitalisation électroniques et du réseau des pharmacies provinciales. Des statistiques descriptives ont servi à analyser les données : les variables catégorielles ont été présentées sous forme de fréquences et de pourcentages; les variables continues ont été analysées et présentées sous forme de moyennes avec les écarts-types et, le cas échéant, sous forme de moyennes avec les écarts interquartiles.

Résultats : Quarante-sept patients, ayant effectué 74 visites en clinique, ont participé à l'étude. Vingt-huit patients (60 %) se conformaient à leur thérapie AOD. Les analyses sanguines de tous les patients ont été effectuées avant chaque rendez-vous en clinique. Le temps moyen entre le premier et le deuxième ensemble de tests sanguins était de 6,2 mois (écart-type standard [ET] 1,4), et de 5,1 mois (ET 1) entre le deuxième et le troisième. Aucun épisode de TEV ou d'hémorragie importante n'a eu lieu. Il y a eu un accident cérébrovasculaire (3,2 événements par 100 années-personnes; intervalle de confiance [IC] à 95 % 0,2–15,7) et 5 épisodes de saignements non majeurs et cliniquement pertinents (12,8 événements par 100 années-personnes, IC 95 % 4,1–30,1). Les pharmaciens ont décelé 51 problèmes lors des rendez-vous en clinique; parmi ceux-ci, 48 étaient liés aux médicaments. Il a fallu faire appel au médecin du service des thromboses pour résoudre 8 (16 %) problèmes. Une brève discussion entre ce médecin et le pharmacien a été nécessaire pour résoudre 30 (59 %) problèmes et 13 (25 %) ont été réglés uniquement par le pharmacien.

Conclusions : Cette étude décrivait la mise en place et les résultats d'une nouvelle clinique AOD dirigée par les pharmaciens. Les patients de la clinique ont subi une analyse sanguine aux intervalles recommandés et ont reçu des conseils sur l'adhésion et les effets indésirables; les patients ont donc bénéficié d'un suivi conforme aux lignes directrices.

Mots-clés : anticoagulant, anticoagulant oral direct, contrôle des médicaments

INTRODUCTION

Anticoagulants are used to prevent and treat venous thromboembolism (VTE) and to reduce the risk of stroke in patients with nonvalvular atrial fibrillation.[1,2] For decades, warfarin has been the main oral drug used for anticoagulation. However, the metabolism of warfarin varies among individuals, and many drug–drug interactions and drug–diet interactions can affect its safety and efficacy, leading to complications such as bleeding and thromboembolic events.[3] Pharmacists have been successfully managing anticoagulant therapy, primarily warfarin, by leading specialized outpatient anticoagulation management services. A recent systematic review showed that pharmacist-managed outpatient anticoagulation services improve anticoagulation control, decrease bleeding and thromboembolic events, and decrease utilization of health care resources.[4]

Since 2009, four new oral anticoagulants have been introduced—apixaban, rivaroxaban, edoxaban, and dabigatran—which are collectively termed the direct oral anticoagulants (DOACs).[3] The DOACs offer several advantages over warfarin, including more predictable dosing response, reduced need for frequent monitoring and dose adjustments, and fewer drug interactions.[5] Because of these advantages, the DOACs have been recommended as first-line therapy for treatment and prevention of VTE, as well as for stroke prevention in patients with nonvalvular atrial fibrillation.[6,7] This has resulted in an increase in the use of DOACs and a relative decline in the use of warfarin.[8] The more predictable dosing response of DOACs has led many practitioners to believe that routine monitoring of DOACs is unnecessary.[9] However, the DOACs are listed by the US Institute for Safe Medication Practices as high-risk medications and have been associated with a risk of serious adverse effects such as bleeding.[10] In one study of 26 471 patients with atrial fibrillation, less than 50% of patients were adherent to their DOAC therapy.[11] It is therefore recommended that patients receive regular follow-up at 3- to 6-month intervals to enhance adherence and prevent adverse outcomes.[1,9,12-14]

Recent publications have suggested that DOAC monitoring should be incorporated into current anticoagulation clinics.[3,9] Gladstone and others[12] developed a checklist for anticoagulant monitoring based on the expert recommendations of the European Heart Rhythm Association.[15] The checklist defines the following key categories of DOAC monitoring: A, for adherence; B, for bleeding; C, for creatinine clearance; D, for drug interactions; E, for examination; and F, for follow up.[12] Despite extensive evidence showing the value of adding DOAC monitoring to pharmacist-led anticoagulation clinics, there are limited data concerning the implementation of this recommendation.

In October 2017, the Eastern Health Adult Outpatient Thrombosis Service became operational in one health region in Newfoundland and Labrador, Canada. The Thrombosis Service is a comprehensive outpatient thrombosis and anticoagulation management program, which has integrated DOAC monitoring into the service model. The Thrombosis Service consists of several unique but interrelated clinics: an anticoagulation management clinic, a nonurgent thrombosis clinic, a perioperative anticoagulation management clinic, and an outpatient emergency thrombosis clinic. Within these clinics, a multidisciplinary team of thrombosis physicians/hematologists and clinical pharmacists provide care through an evidence-based approach.[2] The Thrombosis Service model utilizes pharmacists as the first point of patient contact.

In the present study, we aimed to describe a new pharmacist-led DOAC monitoring clinic and to assess outcomes for patients who attended the clinic, including adherence to medication therapy, adherence to guideline-recommended frequencies for blood work, and occurrence of adverse and non-adverse events.

METHODS

We completed a retrospective chart review of the pharmacist-led DOAC clinic at the Eastern Health Adult Outpatient Thrombosis Service. The study was approved by the Health Research Ethics Board through Eastern Health.

Study Settings

The pharmacist-led DOAC monitoring clinic, which is part of the Thrombosis Service, is held once weekly. One of the Thrombosis Service pharmacists, from the roster of 3 full-time and 2 part-time pharmacists, is assigned to the clinic. Patients are referred to this clinic for long-term follow-up after it has been determined, during a separate Thrombosis Service clinic visit, that extended therapy with a DOAC is required. The DOAC clinic does not accept outside referrals at this time.

Patients are typically first seen within 6 months after referral, with follow-up planned to continue as long as DOAC therapy is required. The pharmacist determines the frequency of follow-up appointments (typically every 3–12 months). At each appointment, the pharmacist uses a standardized assessment tool, developed by the Thrombosis Service Team according to current evidence[1,9,12–14] (and available upon request to the corresponding author), to assess the patient's status and the potential need for changes to therapy. During each clinic visit, the pharmacist works within the current scope of practice set out by the provincial pharmacy regulatory authority, interviewing the patient, assessing factors such as bleeding risk, thrombotic or bleeding events, and drug interactions, and determining whether the current DOAC dose continues to be appropriate for the patient. The pharmacist also assesses the patient's adherence to the prescribed therapy, assesses the patient for adverse effects, and completes special authorization request forms for the patient if needed. The pharmacist facilitates the

completion of blood work requisitions by obtaining the signature of the Thrombosis Service physician after the requisitions have been prepared. The pharmacist is available for liaison with the patient's pharmacy and family physician as required. Clinic records are scanned and included in the patient's electronic health record. The pharmacist is able to consult the Thrombosis Service physician/hematologist regarding any issues that arise during patient interviews through a brief weekly discussion (approximately 15 minutes). Pharmacists at Eastern Health do not have collaborative practice agreements in place at this time; therefore, during these weekly discussions, the clinic pharmacist also asks the physician for new prescriptions for patients requiring medication changes. Additionally, based on these discussions and the pharmacist's recommendations, the physician decides whether the patient should have an in-person visit with the physician for further assessment.

Participants

All patients who attended their first visit (either scheduled or rebooked) at the DOAC clinic between October 10, 2017, and May 31, 2018, were eligible for inclusion (Figure 1). Patients were identified through electronic hospital records. Patients were excluded if they did not attend their scheduled appointment or if, upon presentation at a DOAC clinic visit, they were found to be receiving a low-molecular-weight heparin or warfarin instead of a DOAC. We were unable to capture whether appointments were original or rebooked, because this information was removed from the system at some point before the time of chart review; however, patients who are not able to attend a given appointment are typically seen during the following clinic. The original study protocol specified that patients who met the inclusion criteria were to be followed until October 30, 2018; however, the follow-up period was later extended to November 30, 2018, in an attempt to capture data for more than 1 clinic appointment for each participant.

Data Collection

Each patient was assigned a unique identifier. The principal investigator (J.H.) collected the data from electronic hospital records using a standardized data collection form. Data collected for the study included demographic characteristics, number of clinic visits, DOAC use, and indication for anticoagulation, as well as data related to prespecified outcomes. Data related to adverse events and blood work could not be collected for patients residing outside the Eastern Health region. Medication refill data were provided by the Newfoundland and Labrador Centre for Health Information from the province's electronic Pharmacy Network database.

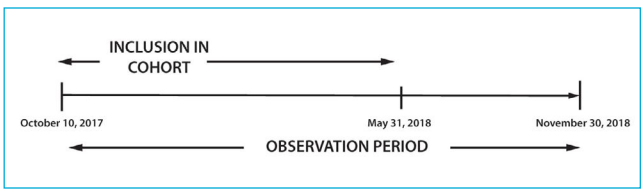

FIGURE 1. Timeline for the study.

Outcome Measures

Adherence

A measure called the proportion of days covered (PDC) was used in determining patients' adherence to their DOAC therapy. The PDC was calculated by dividing the total number of days' supply dispensed during a specific patient's observation period by the total number of days in that patient's observation period and then multiplying by 100; the PDC was capped at 100%.[16] Medication adherence was defined as PDC of at least 80% and nonadherence as PDC less than 80%.[17-20] Adherence was calculated from each patient's first DOAC clinic appointment until October 30, 2018. This measure had an earlier end date than the remainder of the outcome data because the PDC data had to be submitted to the Newfoundland and Labrador Centre for Health Information according to the planned end date of the study (i.e., before the overall observation period of the study was extended). For patients admitted to hospital during the period of evaluation, days spent in hospital were excluded from the PDC calculation. Patients were excluded from this calculation if they had received physician samples of the medication, because the days' supply was not known for samples. Information on whether special authorization was required and completed was extracted and assessed from electronic hospital records.

Follow-up Blood Work

Dates and results of blood tests were obtained from each patient's medical records. The blood tests of interest were white blood cell count, serum creatinine (SCr) level, platelet count, mean corpuscular volume, hemoglobin, activated partial thromboplastin time, and international normalized ratio. These factors are commonly assessed in the monitoring of bleeding and renal function. SCr was used to calculate creatinine clearance (ClCr) using the Cockcroft–Gault equation[21]:

$$\text{ClCr (mL/min)} = \{[1.2 * (140 - \text{age}) * (\text{weight in kg})]/\text{SCr } (\mu\text{mol/L})\} * 0.85 \text{ (if female)}$$

We assessed the adherence to guideline-recommended frequencies of regular blood work and made note of the clinician who ordered the tests (Thrombosis Service physician or another physician). Clinic records were reviewed to determine whether any changes to patients' medication regimens were recommended on the basis of their blood test results.

Adverse Events

The number of adverse events experienced by each patient was extracted from hospital electronic records. Adverse events included hospital admissions or emergency department visits,

VTE events, major bleeding events, and clinically relevant non-major bleeding events. VTE was defined by objective evidence of thrombosis on compression ultrasonography or venography of the leg veins and/or on ventilation-perfusion lung scanning, spiral computed tomography of the pulmonary arteries, or angiography.[22] Bleeding events were defined according to definitions of the International Society on Thrombosis and Haemostasis.[23] Major bleeding was defined as symptomatic presentation of bleeding and at least one of the following: fatal bleeding, bleeding in a critical area or organ (e.g., intra-articular, pericardial, intraocular, intraspinal), bleeding associated with a drop in hemoglobin of 20 g/L or more, or requirement for transfusion of 2 or more units of whole blood or red cells.[23] Clinically relevant non-major bleeding was defined as any sign or symptom of hemorrhage that did not fall into the category of major bleeding but did meet one of the following criteria: patient required medical intervention by a health professional, patient received a face-to-face evaluation, patient was admitted to hospital, or patient required an increase in level of care.[23]

Non-adverse Events

Changes to the medication regimen and medication-related issues identified by clinic staff were obtained from the clinic records. The medication-related issues identified were categorized as follows: nonadherence, dose too high, dose too low, needs additional therapy, unnecessary drug therapy, different drug needed, and adverse drug reaction (defined as a negative reaction to a drug product).[24] For each medication-related issue identified, we assessed whether it was resolved by the pharmacist alone, through subsequent discussion with the Thrombosis Service physician, or through referral to the Thrombosis Service physician's clinic.

Data Analysis

No power calculation was completed because all patients receiving a DOAC and seen in the DOAC clinic during the specified time frame were included. Categorical variables are presented as frequencies and percentages and continuous variables as means with standard deviations (SDs) or medians and interquartile ranges. Adverse events data were analyzed descriptively as binary, count, and time-to-event variables.

RESULTS

Patient Demographics

A total of 47 patients were included in the study (Table 1). The most common DOAC used was rivaroxaban (30 patients [64%]), and the most common indication for an anticoagulant was VTE (44 patients [94%]). The mean follow-up time in the study was 9.1 (SD 2.0) months. All 47 patients had a first clinic visit, 24 patients (of 29 booked [83%]) had a second clinic visit, and 3 patients (of 4 booked [75%]) had a third clinic visit (Table 2). The mean time from the first clinic visit to the second clinic visit was 5.9 (SD 1.3) months, and the mean time between the second and third clinic visits was 5.5 (SD 1.8) months.

Adherence

Twenty-eight (60%) of the patients were adherent to their DOAC therapy (i.e., PDC ≥ 80%). The mean PDC was 79.6% (SD 20.3%). The proportion of patients requiring special authorization for their DOAC declined with each clinic visit (21% [10/47] for clinic visit 1, 4.2% [1/24] for clinic visit 2, and 0% [0/3] for clinic visit 3). However, the need for special authorization was largely unreported in the clinic records. Special authorization was completed at the first clinic appointment for 5 (11%) of the 47 patients (Table 2). It is possible that patients documented as "requiring special authorization" for medication access might not have had the authorization completed by the DOAC clinic pharmacist because it had been completed before the clinic appointment.

TABLE 1. Baseline Characteristics of Patients

Characteristic	No. (%) of Patients[a] (*n* = 47)	
Age (years) (mean ± SD)	60.8 ± 16	
Sex		
Male	21	(45)
Female	26	(55)
DOAC		
Apixaban	12	(26)
Dabigatran	2	(4)
Edoxaban	2	(4)
Rivaroxaban	30	(64)
Other[b]	1	(2)
Indication for DOAC		
Atrial fibrillation	2	(4)
Venous thromboembolism	44	(94)
Cerebral sinovenous thrombosis	1	(2)
Laboratory values at first visit[c]		
WBC ($\times 10^9$ cells/L) (mean ± SD)	7.5 ± 2.4	
CrCl (mL/min) (mean ± SD)	89.89 ± 38.77	
Platelets ($\times 10^9$ cells/L) (mean ± SD)	235 ± 58	
Mean corpuscular volume ($\times 10^{-15}$ L) (mean ± SD)	92.4 ± 5.9	
Hemoglobin (g/dL) (median and IQR)	143.00	(IQR 24.00)
aPTT (s) (median and IQR)	32.35	(IQR 6.32)
INR (median and IQR)	1.26	(IQR 0.34)

aPTT = activated partial thromboplastin time, CrCl = creatinine clearance, DOAC = direct oral anticoagulant, INR = international normalized ratio, IQR = interquartile range, SD = standard deviation, WBC = white blood cells.
[a]Except where indicated otherwise.
[b]One patient discontinued the DOAC on their own before attending the first DOAC clinic visit.
[c]Four patients were excluded from the analysis of laboratory values because their blood work was completed outside of the health authority where the study was conducted.

TABLE 2. Patients' Access to Medication at Each Appointment

Variable	Clinic Visit; No. (%) of Patients					
	Visit 1 (*n* = 47)		Visit 2 (*n* = 24)		Visit 3 (*n* = 3)	
Medication insurance						
No	4	(9)	1	(4)	0	(0)
Yes	31	(66)	14	(58)	1	(33)
Not recorded	11	(23)	8	(33)	2	(67)
Patient receiving samples	1	(2)	1	(4)	0	(0)
Special authorization required						
No	31	(66)	14	(58)	2	(67)
Yes	10	(21)	1	(4)	0	(0)
Not recorded	6	(13)	9	(38)	1	(33)
Special authorization completed						
No	34	(72)	15	(62)	2	(67)
Yes	5	(11)	0	(0)	0	(0)
Not recorded	8	(17)	9	(38)	1	(33)

Regular Blood Work

The blood work analysis included data from 43 patients; the remaining 4 patients were excluded because they lived outside the health authority and subsequent blood work data could not be obtained. For all patients included in the analysis, scheduled blood work was completed before or shortly after each clinic appointment. The mean time between the first and second sets of blood tests was 6.2 (SD 1.4) months and between the second and third sets of blood tests was 5.1 (SD 1.0) months.

Most of the blood work was ordered by the Thrombosis Service physician, and most of the patients received the results at their clinic appointment. For the remaining patients, results were not available until after the clinic appointment, and there was no documentation as to how their results were communicated, given that telephone calls were not documented. Changes in laboratory values between clinic visits were not statistically significant during the period of observation and did not necessitate any changes to patients' medication regimens.

Adverse Events

During the observation period, there were no VTE events. There was 1 thromboembolic event, a cerebrovascular accident in a patient who was taking a DOAC for atrial fibrillation (overall rate 3.2 events per 100 person-years, 95% confidence interval [CI] 0.2–15.7) (Table 3). In addition, there were 5 bleeding events, all of which were classified as clinically significant non-major bleeding (12.8 events per 100 person-years, 95% CI 4.1–30.1). Of these 5 bleeding events, 2 occurred in the same patient. From the electronic hospital records available, 1 death was identified during the observation period, due to renal failure. We observed 17 hospital admissions and 45 emergency department visits. Only 1 (6%) of the 17 hospital admissions was related to

TABLE 3. Adverse Outcomes during Observation Period[a]

Outcome	No. (%)[b]	
No. of hospital admissions/patient	*n* = 43 patients	
None	34	(79)
1	5	(12)
≥ 2	4	(9)
Reason for hospital admission	*n* = 17 admissions	
Related to other thromboembolic events[c]	1	(6)
Unrelated to VTE or bleeding	16	(94)
No. of ED visits/patient	*n* = 43 patients	
None	25	(58)
1	6	(14)
≥ 2	12	(28)
Reason for ED visit	*n* = 45 ED visits	
Related to other thromboembolic events[c]	1	(2)
Related to bleeding	4	(9)
Unrelated to VTE or bleeding	40	(89)
Other thromboembolic events[c]	1 (3.2 per 100 PYs, 95% CI 0.2–15.7)	
Bleeding events[d]		
Major bleeding	0	
Clinically significant non-major bleeding	4 (12.8 per 100 PYs, 95% CI 4.1–30.1)	

CI = confidence interval, ED = emergency department, PY = person-year, VTE = venous thromboembolism.

[a]The data in this table are based on 43 patients; 4 patients were excluded from the outcome analysis because they lived outside the health authority, and information on outcomes was not accessible through hospital records.

[b]Except where indicated otherwise.

[c]The single event in the category "other thromboembolic events" was an arterial event (specifically cerebrovascular accident) in a patient with atrial fibrillation and proportion of days covered less than 80%. This event led to an ED visit, as well as hospital admission, and is included in the count for each of these outcomes.

[d]There were 5 bleeding episodes in total; however, 2 of these episodes occurred in the same patient. For calculation of the frequency per 100 PYs, patients were excluded after their first event. Therefore, only 4 of the bleeding events were included in this calculation.

a thromboembolic event. Of the 45 emergency department visits, 1 (2%) was related to the cerebrovascular accident, and 4 (9%) were related to bleeding (Table 3).

Non-adverse events

Many of the changes made to patients' medication regimens occurred at the first clinic visit. Of 47 patients, 7 (15%) required changes to their medication regimens at their first appointment. The most common type of change was a dose change.

During the observation period, 51 issues were identified by the pharmacist (Table 4). Of these, 48 (94%) were medication-related. The most common type of medication-related issue identified was an adverse drug reaction (35%). About 25% (13/51) of the issues identified were resolved by the pharmacist alone, whereas discussion with the Thrombosis Service physician was required to resolve 30 (59%) of the issues, and referral to the clinic of the Thrombosis Service physician was required to resolve the remaining 8 (16%) issues. The most common reason for referral was a potential adverse drug reaction (38% [3/8]).

DISCUSSION

Several studies have shown that patient education, monitoring, and long-term follow-up reduce nonadherence to medication therapy and improve anticoagulation management.[25-28] Despite extensive evidence showing the value of adding DOAC monitoring to pharmacy-led anticoagulation clinics, few studies describing the implementation of this recommendation have been conducted.[3,9,12]

One study of 26 471 patients with atrial fibrillation showed that less than 50% of the patients were adherent to their DOAC therapy.[11] Recent publications have recommended that patients receive regular monitoring and follow-up at 3- to 6-month intervals to enhance adherence and to prevent adverse outcomes.[1,9,12-14] The patients at the Eastern Health pharmacist-led DOAC clinic received this recommended follow-up. However, we measured adherence in terms of the PDC, and the PDC calculation has many limitations; as such, we may have underestimated the level of adherence. For example, if a patient received a 90-day supply just before their first DOAC clinic appointment, those 90 days would not be counted in the calculation of PDC, which could lead to inaccurate representation of their adherence.

All patients in the current study had blood work completed for each clinic visit. The time between blood tests for patients with a second and possibly third set of laboratory tests during the observation period was 5–6 months. This interval is in line with recommendations for frequency of blood work for patients receiving long-term DOAC therapy.[9,15] Recommendations for DOAC monitoring include assessing renal function every 3–12 months, depending on the patient's creatinine clearance.[9,15] It has been shown that a decrease in estimated glomerular filtration rate is associated with an increase in risk of bleeding and thromboembolic events.[29] Monitoring of renal function is especially important for patients who are taking a DOAC, because poor renal function may necessitate a dose reduction or a change in therapy.[9] Patients were excluded from the major randomized clinical trials of DOACs if their creatinine clearance was less than 30 mL/min (25 mL/min for apixaban).[30-33] Current product monographs for rivaroxaban and apixaban state that they can be used with caution in patients with creatinine clearance greater than 15 mL/min.[34,35] One study compared

TABLE 4. Types of Real or Potential Drug Therapy Problems and Non–Drug-Related Issues Identified, Method of Resolution, and Proportion Leading to Change in the Medication Regimen

	Method of Resolution; No. (%) of Problems[a]									
Variable	Overall		Resolved by Pharmacist		Discussed with Physician		Referral to Physician		Resulted in Change to Medication	
No. of issues identified	51	(100)	13	(25)	30	(59)	8	(16)	9	(18)
Medication-related	48	(94)	13	(27)	28	(58)	7	(15)	9	(19)
Adverse drug reaction	18	(35)	10	(56)	5	(28)	3	(17)	0	(0)
Dose too high	10	(20)	0	(0)	9	(90)	1	(10)	6	(60)
Dose too low	2	(4)	0	(0)	2	(100)	0	(0)	2	(100)
Different drug needed	4	(8)	0	(0)	3	(75)	1	(25)	1	(25)
Nonadherence	13	(25)	3	(23)	8	(62)	2	(15)	0	(0)
Unnecessary drug therapy	1	(2)	0	(0)	1	(100)	0	(0)	0	(0)
Not medication-related	3	(6)	0	(0)	2	(67)	1	(33)	0	(0)

[a]For the "Overall" column, percentages are calculated in relation to the total sample (n = 51). For all other columns, percentages are calculated in relation to number of issues for that row, as shown in the "Overall" column.

the outcomes of patients treated with dabigatran followed by either a pharmacist-managed anticoagulant clinic or usual care and showed that the proportion of patients who underwent baseline laboratory testing before initiation of dabigatran was higher in the anticoagulant clinic group. This may indicate that pharmacists could improve patient monitoring by assessing laboratory values more closely.[36]

We found no episode of major bleeding during the period of observation in this study. However, our study was limited by a small sample size and short period of observation, and thus it was not powered for comparison with event rates reported in the literature. The stroke event in our study occurred in a patient with atrial fibrillation who had inadequate adherence to DOAC therapy.

The most common medication-related issue identified during the observation period was "adverse reaction". However, none of the adverse reactions led to a change in the medication regimen. The issues identified in the study were both real and potential, and upon further investigation, many of these issues were deemed unrelated to the DOAC. For adverse reactions deemed unrelated to the DOAC or the reason for their clinic visit, patients were referred to their primary care provider. Most of the changes to medication regimens made during clinic visits were decreases in dose, in accordance with recent evidence that a dose decrease may be recommended for some individuals meeting certain criteria.[37,38] Of 51 issues identified, only 8 (16%) required referral to the Thrombosis Service physician. The remainder of the issues were resolved by the pharmacist alone or through the brief weekly discussion with the physician. This provides a potential for savings of cost, as well as time, allowing the specialists to spend more time with patients who require more urgent care.

This study had a number of strengths. Given that little evidence is available on the implementation of a pharmacist-led DOAC clinic, this study presents novel information not widely reported in the literature. Many variables have been described, providing a wide range of information about the pharmacist-led DOAC clinic. In particular, the proportion of patients receiving blood work regularly in pharmacist-led DOAC clinics has not previously been reported.

This study also had several limitations. It did not include a comparator group, which limits our ability to draw conclusions about causation and impact relative to usual care. Further studies should be conducted to compare variables such as adherence, regular blood work, and adverse events in a pharmacist-led DOAC clinic and in usual care (e.g., patients followed by their family physician). Another limitation is that the electronic health record does not contain information about patients' adverse event–related visits to their general practitioner or clinics outside the health authority. As such, our study did not include adverse events investigated in any setting outside the health authority. As mentioned above, there are limitations to the use of PDC in evaluating adherence. This method uses refill dates to estimate adherence and does not confirm actual drug consumption. The mean follow-up time was only 9 months, so patients with yearly follow-up had only one clinic visit during the course of the study. The study also had a relatively small sample size, likely because the intake period occurred during the first 7 months after the clinic was opened, when the number of patients being seen was still in the growth stage. VTE, stroke, and bleeding are rare events. Therefore, the confidence intervals for incidence rate estimates were wide. In the future, a larger study with a longer observation period would be beneficial to draw firmer conclusions.

CONCLUSION

The use of DOACs has been increasing rapidly since 2011.[8] It is recommended that patients taking DOACs undergo regular follow-up to improve adherence and decrease the rate of adverse events. This study has described the process for and results of implementation of a pharmacist-led DOAC clinic, which uses pharmacists as the first point of contact for regular follow-up of long-term anticoagulation. Patients being followed in this clinic had blood work performed at guideline-recommended frequencies.[9,11,15,28] Although 1 patient experienced a cerebrovascular accident, no patients experienced major bleeding or VTE. This model for DOAC management provides patients with high-quality follow-up that aligns with guideline recommendations. This descriptive study can be used by clinicians as a guide to initiating similar clinics within their own institutions.

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Correlation between Medication Administration–Related Errors in Patients with Parkinson Disease and Timing of Pharmacy-Led Best Possible Medication Histories

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ABSTRACT

Background: Poor prescribing and incomplete medication administration have been linked to increased lengths of hospitalization for patients with Parkinson disease. The Institute for Safe Medication Practices (ISMP) has recommended that patients with Parkinson disease receive a pharmacy consultation within 2 h of admission to hospital.

Objectives: To examine whether the time for a pharmacy team member to obtain a best possible medication history (BPMH) was associated with administration-related medication errors. The primary outcome was the proportion of doses with a medication error during a patient's admission in relation to the time to completion of the initial BPMH by a registered pharmacist (RPh) or registered pharmacy technician (RPhT). The secondary objective was to compare the proportion of doses with a medication error in relation to whether the BPMH was completed by an RPh or an RPhT.

Methods: This retrospective chart review involved patients with Parkinson disease who were admitted to the medicine services at London Health Sciences Centre from September 30, 2014, to September 30, 2018. Patients were included if they had Parkinson disease and a medication regimen that included levodopa-carbidopa. For all patients, an RPhT or RPh conducted the initial BPMH or updated the BPMH. Pearson correlation analysis was used to determine whether a correlation existed between administration-related errors and completion of the BPMH by a pharmacy staff member.

Results: A total of 84 patients with 104 admissions were included. There was no significant correlation between the time to completion of the initial BPMH by a pharmacy team member and the proportion of doses with medication errors ($p = 0.32$). Although RPhTs completed the BPMHs more quickly than RPhs ($p < 0.001$), there was no significant difference between pharmacy team members in terms of the proportion of doses with medication errors ($p = 0.86$).

Conclusions: Completing a BPMH within 2 h of a patient's admission, as per the ISMP recommendation, is unlikely to affect administration-related medication errors, given that no correlation was identified. Expediting BPMH without addressing other factors is insufficient, and initiatives are required to improve the medication administration process.

Keywords: Parkinson disease, best possible medication history, medication error

RÉSUMÉ

Contexte : La mauvaise prescription et l'administration incomplète de médicaments ont été liées à une augmentation de la durée du séjour à l'hôpital des patients atteints de la maladie de Parkinson. L'Institute for Safe Medication Practices (ISMP) a recommandé que les patients atteints de la maladie de Parkinson obtiennent une consultation en pharmacie dans les 2 heures après leur admission à l'hôpital.

Objectifs : Vérifier si le temps d'attente pour l'obtention, par un membre de l'équipe de la pharmacie, du meilleur schéma thérapeutique possible (MSTP) était associé ou non à des erreurs de médication liées à l'administration. Le résultat principal portait sur la proportion des doses comportant une erreur de médication lors de l'admission d'un patient par rapport au temps nécessaire à un pharmacien ou à un technicien en pharmacie autorisés pour réaliser le MSTP initial. L'objectif secondaire visait à comparer la proportion des doses comportant une erreur de médication entre un MSTP réalisé par un pharmacien autorisé et un MSTP réalisé par un technicien en pharmacie autorisé.

Méthodes : Cet examen rétrospectif des dossiers impliquait des patients atteints de la maladie de Parkinson ayant été admis aux services de médecine au London Health Sciences Centre entre le 30 septembre 2014 et le 30 septembre 2018. Les patients pouvaient participer à l'étude s'ils avaient la maladie de Parkinson et qu'ils suivaient un traitement médicamenteux comprenant du lévodopa-carbidopa. Un pharmacien autorisé ou un technicien en pharmacie autorisé réalisait ou actualisait le MSTP initial de tous les patients. La corrélation de Pearson a servi à déterminer s'il existait une corrélation entre les erreurs liées à l'administration et la réalisation du MSTP par un membre du personnel de la pharmacie.

Résultats : Au total, 84 patients correspondant à 104 admissions ont été inclus dans l'étude. Il n'y avait aucune corrélation importante entre le moment de la réalisation du MSTP initial par un membre du personnel de la pharmacie et la proportion des doses comportant des erreurs de médication ($p = 0,32$). Bien que les techniciens en pharmacie autorisés aient terminé plus rapidement leur MSTP que les pharmaciens autorisés ($p < 0,001$), aucune différence importante n'a été notée entre les membres du personnel de la pharmacie en termes de proportion des doses et d'erreur de médication ($p = 0,86$).

Conclusions : Il est peu probable que la réalisation d'un MSTP dans les 2 heures après l'admission d'un patient, conformément à la recommandation de l'ISMP, ait une influence sur les erreurs de médication liées à l'administration, vu qu'aucune corrélation n'a été décelée. Précipiter la réalisation du MSTP sans aborder les autres facteurs ne suffit pas et des actions sont nécessaires pour améliorer le processus d'administration des médicaments.

Mots-clés : maladie de Parkinson, meilleur schéma thérapeutique possible, erreur de médication

INTRODUCTION

Parkinson disease is a progressive neurodegenerative disorder marked by a constellation of clinical manifestations, including bradykinesia, rigidity, a resting tremor, and postural instability.[1] It is thought to be related to the loss of dopaminergic neurons in the substantia nigra. Dopamine replacement therapy is effective and represents the standard of care for these patients.[1]

Over the years, there has been significant interest in the problem of omission of doses of Parkinson disease–related medications during hospitalization. Martinez-Ramirez and others[2] reviewed data for 212 patients with Parkinson disease over 2 years, looking at medication errors related to the wrong time of administration, dose omission, and the use of contraindicated medications. Patients who experienced delayed administration had longer lengths of stay in hospital, and 20% of patients received a contraindicated dopamine blocker. Similarly, Lertxundi and others[3] examined patients with Parkinson disease in the Basque Country and found that medication errors were associated with increased length of stay and a higher mortality rate. Derry and others[4] examined the management of patients with Parkinson disease on surgical wards over an 18-month period. Of the 51 patients receiving medications for this disorder, 71% had missed doses of their medications. Notably, 34% missed more than 10% of prescribed doses. Overall, 12% of all prescribed medication doses for Parkinson disease were missed.[4]

Poor prescribing and incomplete drug administration led to the development of the "ACT on Time" program by Parkinson Canada to improve patients' quality of life and educate health care providers.[5] The program provides patients with educational materials, including a medical alert card, a list of medications to avoid, and a diary to track medications taken and their response, as well as information that the patient should take when visiting the hospital.[5] The goal is to empower patients to advocate for themselves and collaborate with health care providers to ensure that medications are provided at appropriate times. In addition, the Institute for Safe Medication Practices (ISMP) published recommendations for managing the care of patients with Parkinson disease during hospitalization; these recommendations included stocking common Parkinson disease medications to avoid delays associated with use of nonformulary medications, avoiding contraindicated medications, and providing surgery at optimal times (earlier in the day) to avoid delays in medication administration.[6] Notably, one of the recommendations related to expediting pharmacy consultations is to complete the best possible medication history (BPMH) within 2 h of admission.[6] There is currently a lack of literature to support prioritizing patients with Parkinson disease for BPMH, as part of the medication reconciliation process, and to indicate whether the time to completion of BPMH affects patient care.

At the London Health Sciences Centre (LHSC), all members of the health care team are responsible for documenting the BPMH to contribute to an effective medication reconciliation process. Evidence from previous studies of medication reconciliation suggests that registered pharmacists (RPhs) identify significantly more medication discrepancies and consistently document specific doses and schedules to a greater extent than physicians and other health care providers.[7] Further research now supports the utilization of registered pharmacy technicians (RPhTs) to complete BPMHs in various areas of the hospital, as there do not appear to be significant differences between RPhs and RPhTs in terms of medication discrepancies identified.[8] Current evidence supports the RPhT role in the emergency department in reducing potential adverse drug events and identifying medication discrepancies.[8] RPhTs have assisted in the completion of BPMHs in the LHSC emergency department since 2014, with priority for patients who will be admitted to hospital. RPhTs currently exercise professional judgment to determine which patients require an expedited BPMH.

The ISMP recommendation for completion of the BPMH within 2 h of admission[6] is a shift from current standards. The purpose of this study was to establish whether there was any relation between the time to completion of the BPMH by a pharmacy team member and the proportion of doses of medications with errors among patients with Parkinson disease. We also examined the proportion of doses with medication errors during a patient's admission in relation to the particular pharmacy professional who obtained the BPMH.

METHODS

This study was a retrospective review of adult patients with Parkinson disease admitted to LHSC's general medicine services from September 30, 2014, to September 30, 2018. Ethics approval was granted by the Office of Research Ethics and the Western Health Research Institute (HSREB ID 113652).

Patients were eligible for inclusion if they had a diagnosis of Parkinson disease, had a medication regimen that included levodopa-carbidopa, and were admitted to the LHSC general medicine services during the study period. For each qualifying admission, the BPMH had to have been performed or updated by a pharmacy team member, specifically an RPhT or RPh. No additional exclusion criteria were applied.

Patients were identified from a drug usage report of levodopa-carbidopa. The electronic chart of each identified patient was accessed (through the patient's medical record number) and then reviewed by a single author (E.C.) to determine whether the patient met the inclusion criteria. The electronic admission and progress notes were used to identify patients with a diagnosis of Parkinson disease as opposed to those with other indications for levodopa-carbidopa. The medication history "snapshot" was reviewed to determine whether an RPhT or RPh was involved in the BPMH during the general

medicine admission. The admission histories were reviewed to determine whether the patient had additional admissions meeting the inclusion criteria. Appendix 1 (available from: https://cjhp.journals.publicknowledgeproject.org/index.php/cjhp/issue/view/202) provides additional information about the data collected from electronic charts.

Length of stay was calculated as the difference between time of admission and time of discharge, expressed as number of days. The time of admission was collected from the record of the emergency department encounter and represented the time of the decision to admit the patient.

The primary outcome was the proportion of doses with medication errors during a patient's admission in relation to the time taken by a pharmacy team member to complete the initial BPMH. Patients could have multiple updates to the BPMH during their stay. The initial BPMH was defined as the first BPMH completed and documented by a pharmacy team member, and the final BPMH was defined as the last BPMH completed and documented by a pharmacy team member. The proportion of doses with medication errors was defined as the total number of doses of antiparkinsonian medication either omitted or administered more than 60 min before or after the scheduled time, divided by the total number of antiparkinsonian medication doses scheduled. The occurrence of errors in timing of administration was determined by reviewing the electronic medication administration record and evaluating whether any antiparkinsonian medications were administered at the wrong time (i.e., > 60 min before or after the scheduled time) and/or completely omitted. Omissions were defined as a nurse not administering the drug when it was scheduled or a medication being recorded in the BPMH but not ordered.

The secondary outcome was the proportion of doses with medication errors during a patient's admission in relation to which pharmacy team member completed the BPMH. Patients were categorized according to whether an RPhT or RPh completed or modified the BPMH. The medication errors identified during medication reconciliation were evaluated to determine whether they involved antiparkinsonian agents or other medications and whether the medications with discrepancies were included in the BPMH. Additionally, data were collected to identify the most common reasons documented for administration-related medication errors.

Descriptive statistics and frequencies were calculated for continuous and categorical variables, respectively. The continuous variable related to specific errors in timing of administration. The categorical variables included whether patients experienced a medication error and the reasons for the error. Pearson correlation analysis was conducted to examine the relation between the proportion of doses with errors and the time to completion of the BPMH. The Student *t* test was used to examine differences in medication errors and time to BPMH completion between RPhTs and RPhs. Values of p less than 0.05 were considered statistically significant.

RESULTS

A total of 249 electronic patient charts were screened (Figure 1); 165 patients were excluded because they did not have Parkinson disease or a pharmacy team member was not involved in their BPMH during the qualifying admission. Eighty-four patients met the inclusion criteria, of whom 16 patients had at least 1 additional qualifying admission. In total, 104 admissions were included in the data analysis.

Table 1 presents the baseline characteristics for admissions that met the inclusion criteria. The mean age was 80.5 years, with approximately half of the patients being male (54%); for 65% of the admissions, the patient resided at home before admission to hospital. The average number of

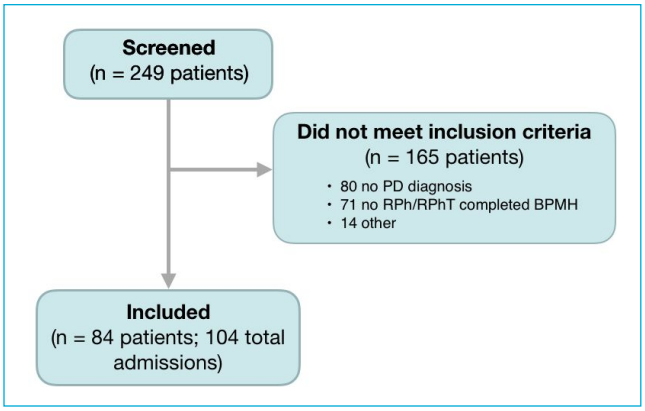

FIGURE 1. Patient flow diagram and exclusion criteria. BPMH = best possible medication history, PD = Parkinson disease, RPh = registered pharmacist, RPhT = registered pharmacy technician.

TABLE 1. Baseline Characteristics

Characteristic	No. (%) of Admissions[a] (*n* = 104)
Age (years) (mean ± SD)	80.5 ± 10.1
Sex, male	56 (54)
No. of medical comorbidities (mean ± SD)	7 ± 2.5
No. of administrations per day (mean ± SD)	4 ± 2.2
Prior disposition	
Home	68 (65)
Long-term care	31 (30)
Other	5 (5)
Initiation of BPMH	
Medical resident	41 (39)
Registered pharmacy technician	28 (27)
Registered pharmacist	28 (27)
Other	7 (7)
Length of stay (days) (mean ± SD)	5.04 ± 5.9

BPMH = best possible medication history, SD = standard deviation.
[a]Except where indicated otherwise. Data are based on a total of 104 admissions for 84 individual patients.

medical comorbidities was 7. The first BPMH was completed by a medical resident for 39% of the 104 admissions, by an RPh for 27%, by an RPhT for 27%, and by a nurse for 7%. The reason for admission was categorized as infection, weakness or functional decline, altered level of consciousness, cardiovascular-related, or other. The most common reason for admission was infection (37%), followed by weakness or functional decline (31%) (Table 2). The mean length of stay was 5.04 days.

The total number of doses of antiparkinsonian medications scheduled was 2984. Of these scheduled doses, 384 (12.9%) were given at the wrong time. Of the 104 admissions included in the study, 91 (88%) included at least 1 dose that was administered more than 60 min before or after the scheduled time, and 58 (56%) of the admissions had more than 10% of their total doses administered at the wrong time. The most common documented reason for wrong administration time was "clinical judgment", which encompassed 30% of all doses administered at the wrong time (Table 3). Of the 2984 scheduled doses, 260 (8.7%) were omitted altogether. The most common reason for omission of a dose was the medication not being ordered in the emergency department (Table 4). Notably, 23 patients had at least 1 antiparkinsonian medication error identified and addressed by a pharmacy team member. The most commonly documented error involved the frequency of levodopa-carbidopa (e.g., initial BPMH stated twice daily, but RPhT changed to 3 times daily).

The primary outcome—the proportion of doses with a medication error during a patient's admission in relation to the time taken by a pharmacy team member to complete the initial BPMH—was not statistically significant (r = –0.098, p = 0.32; Figure 2). Statistical analysis was also completed according to the time when the final BPMH was completed by a pharmacy team member; no correlation was identified with the proportion of doses having medication errors (r = –0.094, p = 0.34; data not shown).

To address the secondary objective, the time to completion of the initial BPMH was compared between RPhTs and RPhs. RPhTs completed the BPMH significantly more quickly than RPhs: 9.6 versus 35.2 h from the time of admission (p < 0.001; Figure 3). Further analysis of the time to completion of initial BPMH was conducted to examine whether there was a reduction in the proportion of doses with medication errors for patients whose BPMH was completed by an RPhT. Although RPhTs completed the BPMH more quickly, the proportion of doses with medication errors did not differ significantly (p = 0.86; Figure 4).

TABLE 2. Reason for Admission

Reason for Admission	No. (%) of Admissions (n = 104)	
Infection	38	(37)
Weakness/functional decline	32	(31)
Cardiovascular	8	(8)
Altered level of consciousness	7	(7)
Bleeding-related	5	(5)
Other	14	(13)

TABLE 3. Reason for Wrong Time of Dose Administration

Reason for Wrong Administration Time	No. (%) of Instances (n = 384)	
Clinical judgment	114	(30)
Incorrect schedule	90	(23)
Patient unavailable	53	(14)
Medication unavailable	51	(13)
Other	76	(20)

DISCUSSION

Delays in administration of antiparkinsonian medications are a significant concern for patients as they navigate the health care system. It is estimated that 3 of every 4 patients with Parkinson disease will miss doses of their medications

TABLE 4. Reason for Dose Omission

Reason for Omission	No. (%) of Omissions (n = 260)	
Medication not ordered	149	(57)
Medication not appropriate	62	(24)
Medication unavailable	8	(3)
Other	41	(16)

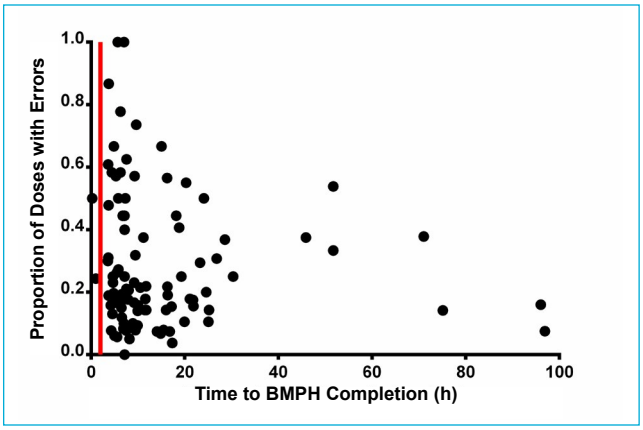

FIGURE 2. Effect of time to complete initial best possible medication history (BPMH) on proportion of doses with a medication error. Each data point represents a single admission. Red line represents the 2-h mark (as recommended by the Institute for Safe Medication Practices[6]). Pearson r = –0.098; p = 0.32.

during a hospital admission.[4] Without timely administration of their medications, patients may experience worsening of their symptoms and a prolonged length of stay.[2-4] ISMP created recommendations for patients with Parkinson disease who are admitted to hospital, including a pharmacy consultation to complete the BPMH within 2 h of admission.[6] To our knowledge, this is the first study examining the roles of RPhs and RPhTs in completing medication reviews with the goal of reducing medication administration–related errors. The aim of the study was to determine whether a relation existed between the proportion of doses with medication administration–related errors and the time to BPMH completion by a pharmacy team member.

We found no significant correlation between the time taken by a pharmacy team member to complete the BPMH and the proportion of doses with medication administration–related errors. On average, RPhTs completed the BPMH 9.6 h after admission, compared with 35.2 h for RPhs. There was no statistically significant difference in the proportion of doses with medication administration–related errors between the 2 groups. No pharmacy team member completed the BPMH within 2 h of admission, although for a total of 5 patients, BPMH was completed by a health care provider outside the pharmacy team within the recommended 2-h time frame. Therefore, no further analysis was performed to determine whether completion of the BPMH within 2 h of admission made a significant difference in outcome.

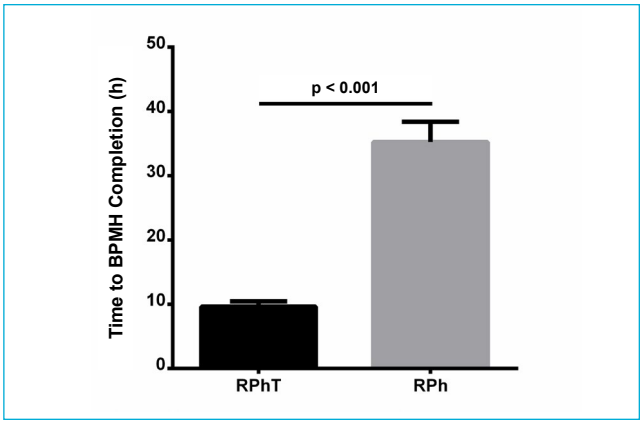

FIGURE 3. Time to completion of best possible medication history (BPMH) by registered pharmacy technicians (RPhT) and registered pharmacists (RPh). Data are shown as means with standard errors of the mean (based on $n = 104$ admissions). The p value was calculated using an unpaired, 2-tailed Student t test.

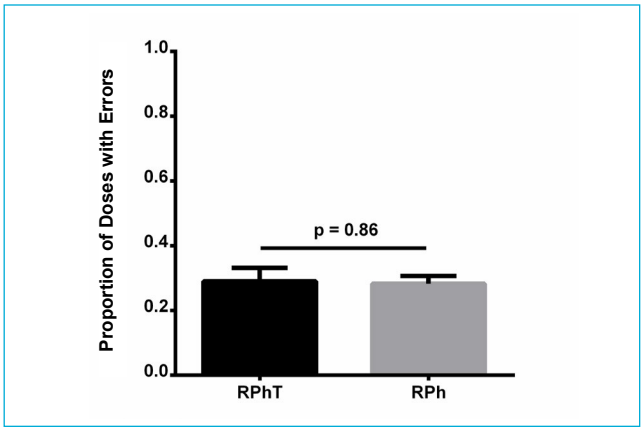

FIGURE 4. Proportion of doses with medication errors for admissions with best possible medication history completed by pharmacy technicians (RPhT) or pharmacists (RPh). Data are shown as means with standard errors of the mean (based on $n = 104$ admissions). The p value was calculated using an unpaired, 2-tailed Student t test.

This study considered 2 different types of medication administration–related errors: errors of timing and complete omission. Timing errors were related to administration of doses more than 60 min from the scheduled time. This timing aligns with previous studies of Parkinson disease and the routine practices of LHSC nurses, whereby they are allowed 60 min before or after the scheduled dosing time to administer any medication. The reasons for wrong timing and dose omissions may indicate factors potentially contributing to the administration-related errors experienced by patients with Parkinson disease. The most commonly documented reason for incorrect timing was clinical judgment (30%), followed by an incorrect schedule (23%). When clinical judgment was reported as the cause of incorrect timing, the administration time ranged from several minutes to hours different from when the dose was due. However, no additional rationale was provided and no further insight was possible, as the electronic charting system does not require nurses to input additional information. Incorrect scheduling of doses reflected provision of medications at the hospital's standardized administration times, rather than according to the patient's individual schedule. The patient's medication schedule was inconsistently documented in the BPMH, and this type of administration error was likely underestimated. Without documentation of the specific home administration schedule and manual modification, the doses are set to be administered according to the hospital's standard administration times. Other reasons for timing errors included patients refusing their medications, nursing staff being busy, and patients being designated to receive nothing by mouth. Further education is required to ensure that health care providers input specific home schedules in the BPMH so that the correct times can be adhered to while the patient is in hospital. It is acknowledged that although staff education may be beneficial, such training would need to be repeated regularly, given the relatively low proportion of patients with Parkinson disease who are admitted to this hospital and the staff turnover rate.

Of the 260 doses that were omitted altogether, 57% were not ordered during the admission process. The proportion of all doses omitted was consistent with previous literature.[2-4] Another source of this type of error was omission of doses before the time of hospital discharge. A large proportion of

patients missed their initial doses in the emergency department, before arriving on the general medicine floor. The data did not capture the number of patients who might have self-administered their medications before presenting to the emergency department. However, to align with the "ACT on Time" initiative, patients with Parkinson disease should be encouraged to bring their medications with them from home, to prevent delay within the initial hours of presentation.[5]

Of the 84 patients included in this study, 23 patients had an antiparkinsonian medication error documented by either an RPh or RPhT. Without the interventions made by the RPhT or RPh, it is hypothesized that a larger number of medication errors would have occurred. These interventions included updating the hospital's records to correctly reflect the patient's home administration times or frequency of administration and the addition of agents that were missed on the initial BPMH. The definition of "medication error" in this study pertained to the timing and omission of doses. This study did not assess medication errors involving different strengths of medications or the number of tablets to be administered. In addition, we did not consider the use of dopamine antagonists, which are contraindicated for patients with Parkinson disease. In other studies,[3,4,9] the use of contraindicated medications was a common type of medication error measured and has been reported to occur in as many as one-quarter of patients. Despite the limitations resulting from the retrospective design of this study, the data demonstrate current challenges in the medication management of patients with Parkinson disease. No clinical outcome data were collected, as such data were not within the scope of the study.

CONCLUSION

Timely administration of medication to hospitalized patients with Parkinson disease remains a challenge. A growing body of evidence has tied delays in administration of antiparkinsonian medication to prolonged length of stay in hospital, mortality, and worsening of the disease. ISMP published several recommendations to reduce medication administration errors in this patient population, including expedited medication reconciliation (within 2 h). In the current study, only 5 patients had BPMH completed within this recommended time frame. Rather than targeting a specific time frame, efforts should be made to ensure that a high-quality review is conducted, to facilitate the medication reconciliation process. Expediting the BPMH without addressing other sources of error is insufficient, and additional initiatives are required to improve the medication-use process.

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Profile of Antimicrobial Use in the Pediatric Population of a University Hospital Centre, 2015/16 to 2018/19

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ABSTRACT

Background: Antimicrobial stewardship is a standard practice in health facilities to reduce both the misuse of antimicrobials and the risk of resistance.

Objective: To determine the profile of antimicrobial use in the pediatric population of a university hospital centre from 2015/16 to 2018/19.

Methods: In this retrospective, descriptive, cross-sectional study, the pharmacy information system was used to determine the number of days of therapy (DOTs) and the defined daily dose (DDD) per 1000 patient-days (PDs) for each antimicrobial and for specified care units in each year of the study period. For each measure, the ratio of 2018/19 to 2015/16 values was also calculated (and expressed as a proportion); where the value of this proportion was ≤ 0.8 or ≥ 1.2 (indicating a substantial change over the study period), an explanatory rating was assigned by consensus.

Results: Over the study period, 94 antimicrobial agents were available at the study hospital: 70 antibiotics (including antiparasitics and antituberculosis drugs), 14 antivirals, and 10 antifungals. The total number of DOTs per 1000 PDs declined from 904 in 2015/16 to 867 in 2018/19. The 5 most commonly used antimicrobials over the years, expressed as minimum/maximum DOTs per 1000 PDs, were piperacillin-tazobactam (78/105), trimethoprim-sulfamethoxazole (74/84), ampicillin (51/69), vancomycin (53/68), and cefotaxime (55/58). In the same period, the care units with the most antimicrobial use (expressed as minimum/maximum DOTs per 1000 PDs) were hematology-oncology (2529/2723), pediatrics (1006/1408), and pediatric intensive care (1328/1717).

Conclusions: This study showed generally stable consumption of antimicrobials from 2015/16 to 2018/19 in a Canadian mother-and-child university hospital centre. Although consumption was also stable within drug groups (antibiotics, antivirals, and antifungals), there were important changes over time for some individual drugs. Several factors may explain these variations, including disruptions in supply, changes in practice, and changes in the prevalence of infections. Surveillance of antimicrobial use is an essential component of an antimicrobial stewardship program.

Keywords: antimicrobial stewardship, antimicrobial therapy, defined daily dose, treatment duration, pediatrics

RÉSUMÉ

Contexte : La gestion des antimicrobiens est une pratique courante dans les centres hospitaliers afin de réduire l'utilisation inappropriée des antimicrobiens et le risque de résistance.

Objectif : Décrire l'évolution de l'utilisation des antimicrobiens dans un centre hospitalier universitaire de 2015-16 à 2018-19.

Méthodes : Dans cette étude rétrospective, descriptive et transversale, les dossiers pharmacologiques ont servi à déterminer le nombre de jours de traitement (NJT) et la dose définie journalière (DDD) par 1000 jours-présence (JP) pour chaque antimicrobien et pour chaque unité de soins par année de l'étude. Pour chaque mesure, on a également comparé le ratio de 2018-19 à celui de 2015-16, qui est exprimé en proportion; lorsque la valeur de cette proportion était ≤ 0,8 ou ≥ 1,2, ce qui indiquait un changement important durant la période de l'étude, une note explicative a été attribuée par consensus.

Résultats : Durant la période à l'étude, 94 antimicrobiens ont été disponibles dans notre centre : 70 antibiotiques (dont les antiparasitaires et les antituberculeux), 14 antiviraux et 10 antifongiques. Le nombre total de NJT par 1000 JP a diminué de 904 en 2015-16 à 867 en 2018-19. Les cinq antimicrobiens utilisés le plus fréquemment et présentés en minimum / maximum de NJT par 1000 JP étaient les suivants : piperacilline-tazobactam (78/105), trimethoprim-sulfamethoxazole (74/84), ampicilline (51/69), vancomycine (53/68) et cefotaxime (55/58). Pendant la même période, les unités de soins qui faisaient la plus grande utilisation d'antimirobiens (exprimée en minimum / maximum de NJT par 1000 JP) étaient hématologie-oncologie (2529/2723), pédiatrie (1006/1408) et soins intensifs pédiatriques (1328/1717).

Conclusions : Cette étude démontre une consommation stable d'antimicrobiens entre 2015-16 et 2018-19 dans un centre hospitalier universitaire mère-enfant canadien. Malgré le fait que la consommation entre les groupes d'antimicrobiens (antibiotiques, antiviraux, antifongiques) était stable, on a constaté d'importantes variations concernant certains médicaments individuels. Plusieurs facteurs peuvent expliquer cette variation, notamment des ruptures d'approvisionnement, des changements de pratique et des changements dans la prévalence d'infections. La surveillance de la consommation des antimicrobiens est une partie essentielle de tout programme d'antibiogouvernance.

Mots-clés : antibiogouvernance, antibiothérapie, dose définie journalière, durée de traitement, pédiatrie

INTRODUCTION

The World Health Organization and other agencies have correlated antimicrobial use with the development of bacterial resistance to antibiotics.[1-3] As such, information about antimicrobial use is integral to defining the priorities of health system stakeholders at the regional, provincial, territorial, national, and global levels.[1-3]

To limit bacterial resistance to antibiotics, a comprehensive international antimicrobial resistance action program, in which Canada is a key player, was adopted in 2015.[1,4] To support this initiative, a pan-Canadian antimicrobial resistance surveillance system was established in 2017,[4] and Accreditation Canada has made antimicrobial stewardship a required organizational practice.[5] Appropriate use of antimicrobials may help to slow the development of resistance.[6-8] In the province of Quebec, an administrative directive came into effect in 2011 requiring that each health facility survey its use of antibiotics.[9] Extraction and analysis of the number of days of therapy (DOTs) per patient-day (PD) and the number of defined daily doses (DDDs) per PD are mandatory.[10-12] This study aimed to describe the profile of antimicrobial use in the pediatric population of a university hospital centre from 2015/16 to 2018/19. These data will allow the antimicrobial stewardship program of the facility to explore trends in its pediatric population and will generate a basis for future comparisons.

METHODS

Study Design and Population

The main objective of this retrospective, descriptive, cross-sectional study was to profile the use of antimicrobials in the pediatric population of a university hospital centre—specifically, the CHU Sainte-Justine, a 500-bed tertiary care mother-and-child facility in Montréal, Quebec—from 2015/16 to 2018/19. The research protocol was approved by the institution's research ethics board.

Inclusion and Exclusion Criteria

We collected data for the following pediatric inpatient care units: surgery, neonatology, hematology-oncology, pediatrics, psychiatry, rehabilitation, and pediatric intensive care. All patients on these care units were 18 years of age or younger. The obstetrics and gynecology and nursery units were excluded.

All doses of systemic (oral and parenteral) antimicrobials dispensed daily to hospital inpatients between April 1, 2015, and March 31, 2019, were included. Antimicrobial doses administered by nebulization or by topical application were excluded because our pharmacy information system cannot provide reliable data for these routes of administration.

The DDDs used for this study were obtained from the WHO's *ATC/DDD Index*.[13] For antimicrobials with reference DDDs using a unit of measure different from the one used locally, we established conversion factors based on the scientific literature.

The numbers of PDs in each care unit and overall were extracted from the periodic statistical profile of admissions, discharges, and transfers within the institution.

Extraction and Analysis of Data

We extracted antimicrobial consumption data from the institution's pharmacy information system (GesphaRx, CGSI Solutions TI Inc). More specifically, we used Structured Query Language queries to determine the number of DOTs and DDDs for each antimicrobial and for each care unit.

From these data, we first established the profile of admission volume, number of DOTs, and number of DDDs. We then calculated, for each antimicrobial, the number of DOTs per 1000 PDs and the number of DDDs per 1000 PDs in each year of the study period (2015/16 to 2018/19). We also established the number of DDDs and the number of DOTs per 1000 PDs by care unit for each year. For each measure, we compared the values for the first and last years of the study; the comparison was calculated as the ratio of the value in the last year to the value in the first year, expressed as a proportion. Any proportion ≤ 0.8 or ≥ 1.2 was deemed, by consensus, to represent a substantial variation over time requiring assessment by the antimicrobial stewardship committee. For cases in which the value of DOT or DDD in 2015/16 was zero, a value of 0.1 was arbitrarily assigned to allow calculation of the ratio in relation to 2018/19 (given that the value for 2015/16 appears in the denominator for calculating this ratio). To explain changes in the ratio from the first to last years of the study period, we assigned a rating based on the following choices: out of stock, change in practice, change in prevalence of the infection, no explanation identified, or variation not substantial.

Only descriptive statistical analyses were performed.

RESULTS

From 2015/16 to 2018/19, a total of 94 antimicrobials were listed in our local drug formulary: 70 antibiotics (including antiparasitics and antituberculosis drugs), 14 antivirals, and 10 antifungals. Detailed results are not presented for the 32 of these 94 antimicrobials that were not used during the study period.

Table 1 shows that admission volumes, as well as numbers of DOTs and DDDs, remained constant over the study period.

Table 2 presents the number of DOTs per 1000 PDs for the individual antimicrobials used in each year in the study period. The 5 most commonly used antimicrobials over the years (in terms of DOTs per 1000 PDs) were piperacillin-tazobactam, trimethoprim-sulfamethoxazole, ampicillin, vancomycin, and cefotaxime. There was no substantial variation over time for all antimicrobials as a group (ratio 1.0 for comparison of last year to first year of the study period)

TABLE 1. Profile of Admission Volumes, Days of Therapy (DOTs), and Defined Daily Doses (DDDs)

Year	No. of Admissions	No. of Patient-Days	No. of DOTs	No. of DDDs
2015/16	11 031	91 211	82 421	48 946
2016/17	10 691	90 632	79 949	43 977
2017/18	11 041	91 532	78 164	49 149
2018/19	10 901	92 654	80 330	50 252
Total	43 664	366 029	320 864	192 324
Annual average	10 916	91 507	80 216	48 081

TABLE 2 (Part 1 of 2). Number of Days of Therapy (DOTs) per 1000 Patient-Days (PDs) by Antimicrobial, 2015/16 to 2018/19

Antimicrobial[a]	Year; DOTs per 1000 PDs				Ratio 2018/19 to 2015/16[c]	Explanatory Rating[d]
	2015/16[b]	2016/17	2017/18	2018/19		
Antibiotics						
Amikacin	1	0	1	2	2.0	D
Amoxicillin	40	38	39	38	1.0	E
Amoxicillin-clavulanic acid	18	18	19	21	1.2	B
Ampicillin	69	65	57	51	0.7	A
Azithromycin	5	6	6	7	1.4	B
Cefazolin	54	53	57	57	1.1	E
Cefixime	1	2	2	4	4.0	A
Cefotaxime	58	56	57	55	0.9	E
Cefoxitin	4	5	4	3	0.8	B
Cefprozil	2	1	2	1	0.5	B
Ceftazidime	14	12	12	9	0.6	B
Ceftriaxone	14	16	18	17	1.2	D
Cephalexin	14	16	15	16	1.1	E
Ciprofloxacin	12	12	13	12	1.0	E
Clarithromycin	16	10	11	10	0.6	B
Clindamycin	23	21	22	25	1.1	E
Cloxacillin	23	21	19	19	0.8	D
Colistimethate	2	2	1	1	0.5	D
Dapsone	0.1	0	0	1	10.0	D
Doxycycline	1	1	2	1	1.0	E
Ertapenem	0.1	0	1	1	10.0	D
Erythromycin	0.1	1	1	1	10.0	D
Ethambutol	1	2	1	1	1.0	E
Gentamycin	31	28	24	21	0.7	A, B
Imipenem	0.1	0	1	1	10.0	D
Isoniazid	2	3	1	1	0.5	C
Levofloxacin	9	9	8	11	1.2	B
Linezolid	9	8	3	2	0.2	B
Meropenem	20	21	26	23	1.2	A
Metronidazole	16	16	14	10	0.6	A

continued on page 24

TABLE 2 (Part 2 of 2). Number of Days of Therapy (DOTs) per 1000 Patient-Days (PDs) by Antimicrobial, 2015/16 to 2018/19

Antimicrobial[a]	Year; DOTs per 1000 PDs				Ratio 2018/19 to 2015/16[c]	Explanatory Rating[d]
	2015/16[b]	2016/17	2017/18	2018/19		
Minocycline	2	1	1	2	1.0	E
Nitrofurantoin	3	1	2	1	0.3	D
Penicillin G	5	3	4	3	0.6	D
Penicillin V	2	1	3	5	2.5	D
Pentamidine	5	5	6	5	1.0	E
Piperacillin	1	0	5	0	0.0	A
Piperacillin-tazobactam	81	90	78	105	1.3	A
Pyrazinamide	1	1	0	0	0.0	C
Rifampicin	4	4	2	3	0.8	C
Sulfasalazine	0.1	1	0	3	30.0	D
Tigecycline	0.1	0	0	1	10.0	D
Tobramycin	63	47	44	31	0.5	A, B
Trimethoprim-sulfamethoxazole	77	84	74	82	1.1	E
Vancomycin	53	53	57	68	1.3	B
Subtotal	756	734	713	731	1.0	E
Antivirals						
Acyclovir	23	20	23	16	0.7	B
Cidofovir	1	2	1	0	0.0	C
Famciclovir	12	12	19	21	1.8	B, C
Foscarnet	1	1	3	1	1.0	E
Ganciclovir	0.1	3	3	3	30.0	B, C
Oseltamivir	8	4	6	6	0.8	B
Ribavirin	2	1	0	0	0.0	D
Valacyclovir	3	3	1	5	1.7	B
Valganciclovir	2	5	3	4	2.0	B, C
Zanamivir	0.1	0	0	0	0.0	D
Subtotal	52	51	59	56	1.1	E
Antifungals						
Amphotericin B	5	4	2	4	0.8	D
Caspofungin	18	24	11	2	0.1	B
Fluconazole	55	48	41	37	0.7	B
Itraconazole	2	2	0	0	0.0	C
Micafungin	0.1	2	18	28	280.0	B
Nystatin	5	5	5	4	0.8	D
Posaconazole	1	4	3	2	2.0	B, C
Voriconazole	2	4	2	3	1.5	B, C
Subtotal	88	93	82	80	0.9	E
Total	896	878	854	867	1.0	E

[a]In alphabetical order within each antimicrobial type.
[b]Where the value of DOT in 2015/16 was zero, a value of 0.1 was arbitrarily assigned, to allow calculation of the ratio in relation to 2018/19 (given that the value for 2015/16 appears in the denominator for calculating this ratio). Entries of 0.1 were not included in the subtotals or total reported for 2015/16.
[c]Values of the ratio ≤ 0.8 or ≥ 1.2 were deemed to represent a substantial change over time, with further investigation required.
[d]Explanatory codes: A = out of stock, B = change in practice, C = change in prevalence of the infection, D = no explanation identified, E = variation not substantial.

or by therapeutic class (ratio 1.0 for antibiotics, 1.1 for antivirals, 0.9 for antifungals). However, there were substantial changes in consumption (i.e., ratio ≤ 0.8 or ≥ 1.2 over time) for 33 of the 70 antibiotics in the formulary (47%), 9 of the 14 antivirals (64%), and 8 of the 10 antifungals (80%). For the 50 drugs with substantial changes, as reported in Table 2, the following reasons were assigned, with some drugs having more than one reason for the observed change: drugs being out of stock (8/50), a change in practice (22/50), a change in the prevalence of infection (10/50), or no explanation (17/50). The remaining 12 medications listed in Table 2 did not show any substantial change over time.

Table 3 presents the number of DDDs per 1000 PDs for the individual antimicrobials used in each year in the study

TABLE 3 (Part 1 of 2). Defined Daily Doses (DDDs) per 1000 Patient-Days (PDs) by Antimicrobial, 2015/16 to 2018/19

Antimicrobial[a]	Year; DDDs per 1000 PDs				Ratio 2018/19 to 2015/16[c]	Explanatory Rating[d]
	2015/16[b]	2016/17	2017/18	2018/19		
Antibiotics						
Amikacin	0.1	0	0	2	20.0	D
Amoxicillin	35	29	33	31	0.9	E
Amoxicillin-clavulanic acid	20	22	23	28	1.4	B
Ampicillin	40	34	41	28	0.7	A
Azithromycin	3	4	5	5	1.7	B
Cefazolin	35	36	40	40	1.1	E
Cefixime	1	1	1	2	2.0	A
Cefotaxime	42	37	43	42	1.0	E
Cefoxitin	1	1	1	1	1.0	E
Cefprozil	1	1	1	1	1.0	E
Ceftazidime	15	12	13	10	0.7	B
Ceftriaxone	8	8	10	9	1.1	E
Cephalexin	9	11	10	12	1.3	D
Ciprofloxacin	11	11	14	14	1.3	D
Clarithromycin	11	8	8	7	0.6	B
Clindamycin	12	11	12	13	1.1	E
Cloxacillin	41	27	29	34	0.8	D
Colistimethate	1	2	1	1	1.0	E
Dapsone	0.1	0	0	1	10.0	D
Doxycycline	1	1	2	2	2.0	D
Ertapenem	0.1	0	0	1	10.0	D
Erythromycin	0.1	0	0	0	0.0	D
Ethambutol	1	1	0	0	0.0	D
Gentamycin	2	1	1	1	0.5	A, B
Imipenem	1	0	0	3	3.0	D
Isoniazid	2	2	1	1	0.5	C
Levofloxacin	7	6	7	8	1.1	E
Linezolid	1	1	1	1	1.0	E
Meropenem	19	17	26	24	1.3	A
Metronidazole	8	7	8	6	0.8	A
Minocycline	2	1	1	2	1.0	E

continued on page 26

TABLE 3 (Part 2 of 2). Defined Daily Doses (DDDs) per 1000 Patient-Days (PDs) by Antimicrobial, 2015/16 to 2018/19

Antimicrobial[a]	Year; DDDs per 1000 PDs				Ratio 2018/19 to 2015/16[c]	Explanatory Rating[d]
	2015/16[b]	2016/17	2017/18	2018/19		
Nitrofurantoin	1	0	0	0	0.0	D
Penicillin G	7	3	4	3	0.4	D
Penicillin V	1	0	1	2	2.0	D
Pentamidine	4	4	5	4	1.0	E
Piperacillin	0.1	0	3	0	0.0	A
Piperacillin-tazobactam	36	42	38	55	1.5	A
Pyrazinamide	1	1	0	0	0.0	C
Rifampicin	4	2	1	3	0.8	C
Sulfasalazine	0.1	1	0	1	10.0	D
Tigecycline	0.1	0	0	1	10.0	D
Tobramycin	40	28	30	22	0.6	A, B
Trimethoprim-sulfamethoxazole	6	7	6	7	1.2	D
Vancomycin	30	29	32	40	1.3	B
Subtotal	460	409	452	468	1.0	E
Antivirals						
Acyclovir	4	3	4	2	0.5	B
Cidofovir	1	4	3	0	0.0	C
Famciclovir	10	9	14	16	1.6	B, C
Foscarnet	1	1	1	0	0.0	C
Ganciclovir	2	1	1	2	1.0	E
Oseltamivir	4	2	4	3	0.8	B
Ribavirin	1	0	0	0	0.0	D
Valacyclovir	1	1	0	1	1.0	E
Valganciclovir	2	1	2	1	0.5	B, C
Zanamivir	3	0	7	1	0.3	D
Subtotal	29	22	36	26	0.9	E
Antifungals						
Amphotericin B	4	2	2	2	0.5	D
Caspofungin	12	17	9	1	0.1	B
Fluconazole	23	19	18	18	0.8	B
Itraconazole	2	1	0	0	0.0	C
Micafungin	0.1	0	6	14	140.0	B
Nystatin	4	4	4	2	0.5	D
Posaconazole	1	3	2	2	2.0	B, C
Voriconazole	2	5	2	3	1.5	B, C
Subtotal	48	51	43	42	0.9	E
Total	537	482	531	536	1.0	E

[a]In alphabetical order within each antimicrobial type.
[b]Where the value of DDD in 2015/16 was zero, a value of 0.1 was arbitrarily assigned, to allow calculation of the ratio in relation to 2018/19 (given that the value for 2015/16 appears in the denominator for calculating this ratio). Entries of 0.1 were not included in the subtotals or total reported for 2015/16.
[c]Values of the ratio ≤ 0.8 or ≥ 1.2 were deemed to represent a substantial change over time, with further investigation required.
[d]Explanatory codes: A = out of stock, B = change in practice, C = change in prevalence of the infection, D = no explanation identified, E = variation not substantial.

period. As for DOTs, there was no substantial variation over time for all antimicrobials as a group (ratio 1.0 for comparison of last year to first year of the study period) or by therapeutic class (ratio 1.0 for antibiotics, 0.9 for antivirals, 0.9 for antifungals). However, there were substantial changes in consumption (i.e. ratio ≤ 0.8 or ≥ 1.2 over time) for 32 of the 70 listed in the formulary (46%), 8 of the 14 antivirals (57%), and 8 of the 10 antifungals (80%). For the 48 drugs with substantial changes, as reported in Table 3, the following reasons were assigned, with some drugs having more than one reason for the observed change: drugs being out of stock (8/48), a change in practice (16/48), a change in the prevalence of infection (10/48) and no explanation (20/48). The remaining 14 medications listed in Table 3 did not show any substantial change over time.

Table 4 presents the numbers of DOTs and DDDs per 1000 PDs by care unit from 2015/16 to 2018/19. The care units with the most antimicrobial use over the study period (in terms of DOTs per 1000 PDs) were hematology-oncology, pediatrics, and pediatric intensive care. The numbers of DOTs per 1000 PDs and DDDs per 1000 PDs in the surgical unit were reduced by half over the 4 years of the study, whereas a 40% increase in these measures was observed in the pediatrics unit.

DISCUSSION

In this descriptive study, we have presented a profile of antimicrobial use for the pediatric population of a university hospital centre over the period 2015/16 to 2018/19. The data reported here have been presented and discussed with the hospital's antimicrobial stewardship committee, the pharmacology and therapeutics committee, and groups of clinicians (e.g., physicians, pharmacists) in the form of an annual report.[14,15]

The results of this study highlight that antimicrobial consumption was stable from 2015/16 to 2018/19 and was also stable for 3 specific groups of drugs (i.e., antibiotics, antivirals, and antifungals). Despite this overall stability, the use of certain broad-spectrum antimicrobials increased from 2015/16 to 2018/19 (e.g., for piperacillin-tazobactam, from 81 to 105 DOTs per 1000 PDs; for meropenem, from 20 to 23 DOTs per 1000 PDs; for ertapenem, from 0.1 to 1 DOTs per 1000 PDs). The misuse of broad-spectrum antimicrobials contributes to the development of antimicrobial resistance. However, within the various groups of drugs, there were substantial variations in use for many individual antimicrobials. There may be different reasons for such variations. Given the pediatric study population, these variations are discussed here with reference only to the data for DOTs per 1000 PDs. (The Results section above presents data for DDDs per 1000 PDs as well, because these values are used for inter-institutional comparisons and because this is the standard measure used for the adult population.)

Some of the variations in use of particular antimicrobials over time were attributed to stock shortages; such shortages will generally lead to a decline in the use of the antimicrobial that is in short supply and a corresponding increase in the use of an alternative drug. For example, the DOTs per 1000 PDs increased over time for cefixime (from 1 in 2015/16 to 4 in 2018/19) because there was a shortage of this cephalosporin from July 2014 to September 2015, at the start of the study period. Cephalexin (increase from 14 to 16 DOTs per 1000 PDs from 2015/16 to 2018/19) and amoxicillin-clavulanic acid (increase from 18 to 21 DOTs per 1000 PDs) were used as alternatives to cefixime during the study period. The increase in use of piperacillin-tazobactam (from 81 to 105 DOTs per 1000 PDs from 2015/16 to 2018/19) was related to a partial disruption in stocking this combination medication from 2015 to 2017.

TABLE 4. Days of Therapy (DOTs) and Defined Daily Doses (DDDs) per 1000 Patient-Days (PDs), by Care Unit, 2015/16 to 2018/19

	Year; Rate per 1000 PDs									
	2015/16		2016/17		2018/19		2018/19		Ratio 2018/19 to 2015/16[a]	
Care Unit	DOTs	DDDs	DOTs	DDDs	DOTs	DDDs	DOTs	DDDs	DOTs/1000 PDs	DDDs/1000 PDs
Surgery	883	655	746	524	550	432	451	351	0.5	0.5
Neonatology	519	38	533	41	429	33	433	35	0.8	0.9
Hematology-oncology	2723	1629	2566	1528	2634	1503	2529	1462	0.9	0.9
Pediatrics	1006	779	1006	690	1186	934	1408	1107	1.4	1.4
Psychiatry	29	71	26	19	19	20	20	16	0.7	0.2
Rehabilitation	48	31	35	17	43	32	58	36	1.2	1.2
Pediatric intensive care	1717	922	1535	832	1331	946	1328	838	0.8	0.9

[a]Values of the ratio ≤ 0.8 or ≥ 1.2 were deemed to represent a substantial change over time, with further investigation required.

This shortage contributed to the higher initial use and subsequent decline in use of gentamycin (gradual decrease from 31 DOTs per 1000 PDs in 2015/16 to 21 DOTs per 1000 PDs in 2018/19), tobramycin (gradual decrease from 63 to 31 DOTs per 1000 PDs), and metronidazole (gradual decrease from 16 to 10 DOTs per 1000 PDs), as well as a peak in use of the carbapenem drugs (e.g., for meropenem, 26 DOTs per 1000 PDs in 2017/18; for imipenem, 1 DOT per 1000 PDs in 2017/18 and 2018/19).

Another explanatory factor that we considered involved changes in practice related to the evolution of scientific knowledge, the arrival of new practitioners, and local discussions involving the pharmacology and therapeutics committee and the chief of the pharmacy department. For example, an increase in the use of azithromycin (from 5 to 7 DOTs per 1000 PDs over the study period) was attributable to this drug's anti-inflammatory properties, especially for patients with cystic fibrosis. The increased use of azithromycin in otorhinolaryngology led to a corresponding reduction in the use of clarithromycin (from 16 to 10 DOTs per 1000 PDs). Furthermore, following a change in internal protocol, there was a decrease in the use of ceftazidime (from 14 to 9 DOTs per 1000 PDs) in favour of piperacillin-tazobactam among patients with febrile neutropenia.[16] Finally, the use of linezolid declined (from 9 to 2 DOTs per 1000 PDs) in favour of vancomycin (from 53 to 68 DOTs per 1000 PDs) with the help of a change of protocol. For some years, linezolid has been preferred over vancomycin for treating sepsis in neonatology (given the presence of coagulase-negative staphylococci with reduced susceptibility to vancomycin); however, resistance monitoring has demonstrated the possibility of returning to vancomycin, which has a safer therapeutic index in the pediatric population. There was also an increase in the use of micafungin (from 0.1 to 28 DOTs per 1000 PDs), with a corresponding decrease in the use of caspofungin (from 18 to 2 DOTs per 1000 PDs). Micafungin has a similar efficacy, its use relies on the availability of more safety data for the pediatric population, and it has replaced caspofungin on the study facility's formulary.[17,18] Finally, there was a decrease in the use of fluconazole (from 55 to 37 DOTs per 1000 PDs), also in favour of the echinocandins (e.g., micafungin).[19]

Another reason for changes in the use of certain antimicrobials was a change in the prevalence of certain infections in the study institution. These changes in prevalence were not necessarily experienced at the regional or provincial level. Evolution in the organization of care sometimes leads to shifts in the locations where certain patient groups are treated. For example, there were decreases in the use of isoniazid (from 2 to 1 DOT per 1000 PDs), as well as pyrazinamide and rifampicin, because of the limited number of cases of tuberculosis that were being followed within our institution.[20] There were also slight increases in the use of posaconazole and voriconazole, observed when the institution treated sporadic cases of invasive infection with *Aspergillus* spp.[21] and other filamentous fungi. Finally, there were slight changes in the use of cidofovir, foscarnet, ganciclovir, and valganciclovir because of the limited and variable number of patients with cytomegalovirus infection.[22]

Regarding changes in use by particular care units over the study period, we found increases in the use of antimicrobials in the pediatrics unit (ratio of 2018/19 to 2015/16 = 1.4) and the rehabilitation unit (ratio 1.2). In theory, these increases could be explained by the admission of patients with more complex health problems to the infectious disease and solid organ transplant units. The decrease in DOTs per 1000 PDs in the surgical unit (ratio 0.5) may be related to increased use of polyvalent antimicrobials (such as piperacillin-tazobactam), which generate fewer DOTs than a combination of 3 agents (such as ampicillin, gentamycin, and metronidazole), as well as to changes in internal protocols to reduce the number of postoperative days in hospital.

This study follows a previous study conducted in our institution for the period 2011/12 to 2014/15.[23] In a comparison of the current results with the data from that previous study, we note that the overall number of DOTs per 1000 PDs has decreased from 1068 in 2010/11 to 867 in 2018/19. This substantial decrease is likely related to the effects of the antimicrobial stewardship program (under the direction of the pharmacy and therapeutics committee), which includes targeted interventions for physicians and pharmacists. The decrease in DOTs per 1000 PDs is also associated with increased use of monotherapy rather than combinations of antimicrobials (e.g., piperacillin-tazobactam replacing the triple combination of ampicillin [93.3 DOTs per 1000 PDs in 2010/11 versus 51 DOTs per 1000 PDs in 2018/19], gentamycin [85 versus 21 DOTs per 1000 PDs, respectively], and metronidazole [23.3 versus 10 DOTs per 1000 PDs, respectively]). Antimicrobial stewardship programs need to closely monitor the impact of such changes, since they increase the use of broad-spectrum antibiotics.

This descriptive study had certain limitations. The study was based on antimicrobial dispensing data, but a dispensed dose may not be administered to the patient, for example because of discharge or a change in therapy. Thus, dispensing data may slightly overestimate the number of doses administered. A complete analysis of antimicrobial use should take into account each patient's clinical condition (e.g., therapeutic response, occurrence of adverse effects). The use of DOTs and DDDs per 1000 PDs provides a general profile of usage. The antimicrobial stewardship committee must conduct additional reviews to investigate changes in the use of particular drugs over time that are more difficult to explain.

CONCLUSION

This study has highlighted stable consumption of antimicrobials from 2015/16 to 2018/19 in a Canadian mother-and-child university hospital centre. Although consumption was

stable by type of drug (antibiotics, antivirals, antifungals), there were important variations for some antimicrobials. Several factors can explain these variations, including supply disruptions, changes in practice, and changes in the prevalence of infections. Surveillance of antimicrobial use is an essential component of an antimicrobial stewardship program. This study has provided a comprehensive basis of comparison for antimicrobial stewardship programs interested in studying antimicrobial use in their respective pediatric populations.

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Completeness of Medication Reconciliation Performed by Pediatric Resident Physicians at Hospital Admission for Asthma

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ABSTRACT

Background: Medication errors at hospital admission, though preventable, continue to be common. The process of medication reconciliation has been identified as an important tool in reducing medication errors. The first step in medication reconciliation involves documenting a patient's best possible medication history (BPMH); at the authors' tertiary pediatric hospital, this step is completed at time of admission by resident physicians.

Objectives: To describe and quantify the completeness of admission BPMH by resident physicians for pediatric inpatients with asthma.

Methods: This single-centre, retrospective chart review evaluated documentation of admission medication reconciliation for pediatric inpatients with asthma who were admitted between January 2016 and December 2017. Medication reconciliation forms were deemed incomplete if records for asthma medications were missing drug name, inhaler strength or oral drug dose, directions for use, or evidence of reconciliation.

Results: A total of 241 charts were evaluated, of which 97 (40%) had incomplete documentation for at least 1 medication; in particular, 48 (37%) of the 130 inhaled corticosteroid orders were missing inhaler strength. For most of the charts with incomplete medication history (68% [66/97]), no reason was documented; however, review of the medication reconciliation forms and physician notes revealed that families might have been unsure of a patient's home medications or physicians might have left it to the pharmacy to clarify medication doses.

Conclusions: Documentation of inhaler medications on admission medication reconciliation forms completed by resident physicians for pediatric patients with asthma was often incomplete. Future quality improvement interventions, including resident and patient education, are required at the study institution. Collaboration with pharmacy services is also likely to improve completeness of the medication reconciliation process.

Keywords: medication reconciliation, asthma, pediatrics

RÉSUMÉ

Contexte : Bien qu'elles soient évitables, les erreurs de médication au moment de l'admission à l'hôpital sont encore répandues. Le processus du bilan comparatif des médicaments a été reconnu comme étant un outil important pour réduire ces erreurs. La première étape du bilan comparatif des médicaments vise à décrire le meilleur schéma thérapeutique possible (MSTP) du patient; dans l'hôpital pédiatrique tertiaire des auteurs, les médecins résidents se chargent de cette étape au moment de l'admission.

Objectifs : Décrire et quantifier le degré d'exhaustivité du MSTP réalisé par les médecins résidents pour les patients en pédiatrie souffrant d'asthme.

Méthodes : Cet examen rétrospectif unicentrique des dossiers a permis d'évaluer l'élaboration du bilan comparatif des médicaments à l'admission en pédiatrie des patients souffrant d'asthme entre janvier 2016 et décembre 2017. Les formulaires de bilan comparatif des médicaments étaient jugés incomplets si les dossiers relatifs aux médicaments contre l'asthme n'indiquaient pas le nom du médicament, la force de l'inhalateur ou la dose orale du médicament, le mode d'emploi ou les preuves de conciliation médicamenteuse.

Résultats : L'évaluation portait sur 241 tableaux; au moins 1 médicament manquait dans la description de 97 d'entre eux (40 %); en particulier la force de l'inhalateur ne figurait pas dans 48 (37 %) des 130 ordonnances relatives aux corticostéroïdes administrés par inhalation. La plupart des tableaux dont l'histoire pharmacothérapeutique était incomplète (68 % [66/97]) n'en indiquaient pas la raison; cependant, l'examen des formulaires du bilan comparatif des médicaments et les notes des médecins ont révélé que les familles n'étaient peut-être pas certaines des médicaments que le patient prenait à domicile ou que les médecins auraient pu laisser aux pharmaciens le soin de clarifier les doses.

Conclusions : La description des médicaments administrés au moyen d'inhalateurs au moment de l'admission, figurant sur les formulaires du bilan comparatif des médicaments remplis par les médecins résidents pour les patients en pédiatrie souffrant d'asthme, était souvent incomplète. De futures interventions sur l'amélioration de la qualité, y compris les instructions données au patient et au résident, sont nécessaires dans l'institution où s'est déroulée l'étude. Il est probable que la collaboration avec les services de pharmacie améliorerait l'exhaustivité du processus du bilan comparatif des médicaments.

Mots-clés : bilan comparatif des médicaments, asthme, pédiatrie

INTRODUCTION

Medication errors among pediatric patients upon admission to and discharge from hospital, though preventable, continue to be common.[1] A systematic review evaluating the occurrence of medication discrepancies in the pediatric population found a high rate of discrepancies, ranging from 22% to 73% of patients, mostly related to admissions.[2] Medication reconciliation identifies clinically significant discrepancies for nearly a quarter of the pediatric population.[3] Given that asthma is the leading cause of hospital admission for children,[4] incomplete or inaccurate reconciliation of asthma medications can lead to clinically significant medication errors in a large proportion of the pediatric inpatient population. Errors with asthma medications, including omission of inhaled corticosteroid during admission for asthma exacerbations, have the potential to increase length of stay and overall costs[5]; as such, appropriate medication reconciliation is imperative. However, specific data regarding the accuracy of medication reconciliation for pediatric patients with asthma are sparse.

Medication reconciliation was implemented in 2008 at our academic children's hospital in eastern Canada, which has 60 pediatric medical/surgical beds. Upon admission of any patient to the pediatric medical unit, the medication reconciliation process is initiated by resident physicians and is mandatory upon admission, transfer, and discharge. For each patient, a resident documents the best possible medication history (BPMH) using a preprinted order form. The form prompts the user to consult at least 2 sources, such as patient and family interviews, medical records, the provincial drug information system, or medication bottles. The listed medications are then assessed by the patient's health care team and a decision is made to continue, change, or discontinue the medications as indicated. This form, once signed by the physician, serves as the admission medication order. Typically, the form is then reassessed and reconciled by a pharmacist or a pharmacy technician upon receipt in the pharmacy. As part of their 2-year academic curriculum, resident physicians attend an educational session facilitated by a clinical pharmacist to learn about proper completion of the preprinted order form. Our literature review of medication reconciliation education initiatives targeted toward resident physicians found limited published data on the best way to approach this training.[6-10]

Medication reconciliation data for pediatric asthma are limited, as are data assessing the accuracy of medication reconciliation performed by medical residents, given that most studies to date have evaluated pharmacy-led initiatives.[11] Therefore, this study aimed to assess the completeness of medication reconciliation forms prepared by resident physicians for pediatric inpatients with asthma. We performed a retrospective chart review to quantify and describe the medication discrepancies revealed through our medication reconciliation process and to inform future quality improvement initiatives. We hypothesized, on the basis of clinical observation and literature showing lower rates of accuracy among physicians,[12] that the rate of discrepancies would be high, with the strength of asthma inhaler most frequently omitted on admission medication reconciliation.

METHODS

This study was a single-centre, retrospective chart review of admission documentation (specifically BPMH) for asthma medications completed by resident physicians as part of medication reconciliation. It was approved by the research ethics board at the study institution (project number 1023121). Inpatients with asthma, defined as patients with a primary or secondary admission diagnosis code for asthma who were admitted to intensive care or general medical units between January 2016 and December 2017, were included. A list of medical record numbers for the study period was provided by the health records department; for patients with multiple admissions during the study period, the preprinted order form for admission medication reconciliation for each individual admission was reviewed. The patient charts, which had been scanned to our hospital's clinical information system, were reviewed electronically by a single reviewer (A.M.).

A medication reconciliation form was deemed to be incomplete if records for asthma medications were missing a drug name, the inhaler strength or oral drug dose, directions for use, or evidence of reconciliation (i.e., decision to continue, hold, or discontinue the medication). For incomplete forms, the admission history and physical examination findings, physician progress notes, order sheets, and preliminary discharge summaries were reviewed to determine if the reason for the incomplete medication history had been documented. Patients with asthma who were not taking any medications at home were excluded from the review, and the completeness of documentation for non-asthma medications was not assessed. For the purpose of this review, failure to document strength of salbutamol metered-dose inhaler was not deemed to represent incomplete documentation, because only one strength of this medication is available in Canada.

Data were coded and entered into an Excel spreadsheet (Microsoft Corporation). Descriptive statistics were calculated for demographic data and were used to quantify the number of incomplete forms with missing information for different classes of asthma medications. In addition, descriptive statistics were used to categorize reasons for incomplete medication histories and whether medication orders were clarified before hospital discharge.

RESULTS

A total of 328 charts for pediatric inpatients with asthma admitted between January 2016 and December 2017 were

identified. Of these, 241 charts had asthma medications listed on the admission form and were included for review. Short-acting bronchodilators constituted the most common class of medication, with 235 (98%) of the charts mentioning this class as a home medication. The second most common medication class was inhaled corticosteroids (130 [54%]). More than half (133 [55%]) of the admission forms were completed by first-year medical residents, who provide on-call coverage for the inpatient medical unit at our centre more frequently than later-year residents. Other demographic data are presented in Table 1.

Overall, as outlined in Table 2, 97 (40%) of the 241 forms reviewed had incomplete documentation for at least 1 medication, the most common reasons being missing inhaler strength/drug dose (33% [143 of 437 individual medication orders]) or missing directions for use (19% [84 of 437 individual medication orders). The most frequent class of medications with incomplete documentation was inhaled corticosteroids (n = 130 orders), with 40% incomplete for any reason, 37% missing the inhaler strength, 14% missing directions for use, 2% without reconciliation, and 1% missing the drug name. Overall, documentation was incomplete more often for inhaler medications than for oral medications: 27% (64/235) of forms for short-acting bronchodilators and 24% (6/25) of forms for combination inhalers were incomplete for any reason (Table 3).

The 97 charts with incomplete documentation of medication reconciliation were further reviewed to determine whether the prescriber acknowledged that the medication history was incomplete; for 19% (18/97), such acknowledgement appeared on the medication reconciliation form, and for 13% (13/97), it appeared in the history and physical or progress notes. The remaining 66 charts (68%) had no documented reason for or acknowledgement of the incomplete orders. Reasons for missing information about patients' home medications as recorded in the charts included "patient/family unsure of dose", "parent does not have puffers", "clarify in the morning", and "pharmacy to clarify". Upon review of the 66 charts with incomplete medication reconciliation (excluding the 31 charts with only incomplete salbutamol documentation), 37 (56%) were clarified by pharmacy before discharge, 5 (8%) were clarified by the medical team before discharge, and 24 (36%) were not clarified (Table 4).

TABLE 1. Patient Characteristics

Characteristic	No. (%) of Patients[a]
No. of charts reviewed	241
Patient age (years) (median and IQR)	4 (0–17)
Hospital admission year	
2017	142 (59)
2016	99 (41)
Home medications	
Short-acting bronchodilators	235 (98)
Inhaled corticosteroids	130 (54)
Montelukast	34 (14)
Combination inhaler	25 (10)
Oral corticosteroid	13 (5)
No. of home medications	
1 or 2	156 (65)
3–5	71 (29)
> 5	14 (6)
Level of training of resident documenting medication reconciliation	
Year 1	133 (55)
Year 2	33 (14)
Year 3	46 (19)
Year 4	23 (10)
Staff physician	4 (2)
Not signed	2 (1)
Time when medication reconciliation form was completed	
Weekday day shift	64 (27)
Weekday night shift	116 (48)
Weekend shift	61 (25)

IQR = interquartile range.

DISCUSSION

Similar to results reported from other studies,[2] information was missing for 40% of medication reconciliation forms completed by resident physicians for asthma admissions at our institution. As we anticipated, the information most commonly omitted was the strength of inhalers. In asthma management, where the controller medication is typically administered by inhaler, inaccurate documentation of home inhalers has the potential to cause medication errors, notably

TABLE 2. Frequency of Incomplete Medication Reconciliation Forms and Missing Information

Variable	*n*/*N* (%)
No. of charts reviewed	241
No. of incomplete forms[a]	
Overall	97/241 (40)
2017	51/142 (36)
2016	46/99 (46)
Asthma medication orders (all charts)	437
Charts with missing information	
Missing drug name	2/437 (< 1)
Missing inhaler strength or drug dose	143/437 (33)
Missing directions for use	84/437 (19)
Not reconciled	11/437 (3)

[a] If the only information missing was strength for salbutamol by metered-dose inhaler, the form was deemed to be complete.

TABLE 3. Completeness of Medication Reconciliation Documentation at Time of Admission, by Asthma Medication Class

Variable	No. (%) of Orders Incomplete, by Class
Inhaled corticosteroid	*n* = 130
Total incomplete	52 (40)
Missing drug name	1 (1)
Missing inhaler strength	48 (37)
Missing directions for use	18 (14)
Not reconciled	3 (2)
Short-acting bronchodilators	*n* = 235
Total incomplete	64 (27)
Missing drug name	1 (< 1)
Missing inhaler strength[a]	87 (37)
Missing directions for use	59 (25)
Not reconciled	8 (3)
Montelukast	*n* = 34
Total incomplete	4 (12)
Missing drug name	0 (0)
Missing drug dose	3 (9)
Missing directions for use	4 (12)
Not reconciled	0 (0)
Combination inhaler	*n* = 25
Total incomplete	6 (24)
Missing drug name	0 (0)
Missing inhaler strength	5 (20)
Missing directions for use	2 (8)
Not reconciled	0 (0)
Oral steroid	*n* = 13
Total incomplete	1 (8)
Missing drug name	0 (0)
Missing drug dose	0 (0)
Missing directions for use	1 (8)
Not reconciled	0 (0)

[a]If the only information missing was strength for salbutamol by metered-dose inhaler, the form was deemed to be complete (i.e., not counted in the "total incomplete" for this class).

TABLE 4. Reasons for Incomplete Documentation of Medication Reconciliation and Predischarge Clarification

Variable	No. (%)
Reason for incomplete documentation	*n* = 97 incomplete orders
None documented	66 (68)
Acknowledged incomplete on medication reconciliation form	18 (19)
Acknowledged incomplete on history/physical findings or progress note	13 (13)
Clarification of medication orders before discharge[a]	*n* = 66 orders with no reason documented
By medical team	5 (8)
By pharmacy	37 (56)
Not clarified	24 (36)

[a] Excluding incomplete salbutamol documentation.

delayed treatment if a nurse is unable to administer the medication until the incomplete order has been clarified. Of note, salbutamol documentation was rarely clarified because most patients with acute asthma exacerbation are transitioned to a preprinted order set, with appropriate weight-based salbutamol dosing. However, any delay or omission of inhaled corticosteroids has implications for quality of care and patient safety; for example, prospective data from a double-blind, randomized controlled trial showed that children continuing with inhaled corticosteroid therapy during hospital admission for acute asthma exacerbation may have shorter lengths of stay, with reduced overall costs, than children who do not continue with their home therapy while in hospital.[5] For the large number of orders that remain unclarified at discharge, adverse outcomes (including loss of symptom control or unnecessary risk of adverse effects) may occur if the patient is unintentionally discharged on an incorrect dose of inhaled corticosteroid. Information about home dosing is frequently used by clinical staff to determine the need for escalation of therapy or to assess potential nonadherence as the reason for admission.

In the majority of charts with incomplete medication reconciliation, the reason was not documented. However, previous studies have noted various barriers to documentation, including unreliable sources of medication information and perceived higher-priority tasks that compete for providers' time and attention.[13] Where residents did provide a reason for incomplete medication reconciliation, they most commonly mentioned that patients and families did not know the name or strength of their medications. In multiple admission histories, inhalers were documented by colour, such as "orange and blue puffers", when families were unsure of the product name or strength. These results are concerning, given that published data show poorer symptom control and medication adherence among children of parents who are unable to name their children's asthma inhalers.[14] In our region, physicians can access a provincial drug information system that provides an electronic record of prescriptions dispensed to individual patients. However, according to anecdotal information, physician awareness and use of this system are minimal at our institution. Although use of the drug information system was not formally recorded as part of this study, it was infrequently marked as a source of information on medication reconciliation forms completed by residents. Alternatively, incomplete medication documentation could represent a gap in knowledge among trainees that multiple strengths of inhalers are available.

At our institution, pharmacy was responsible for the majority of predischarge clarifications. However, 36% of incomplete medication reconciliation forms remained unclarified at discharge; many of these discharges occurred on the weekend, when clinical pharmacy services are not

available on the medical ward. Although increasing physicians' competency to perform medication reconciliation is a reasonable solution, most studies have noted little effect of medication reconciliation education directed at medical residents.[6] Given the aforementioned limitation of physicians favouring tasks of higher priority, delegation of medication reconciliation to an alternative health care provider may be a more worthwhile intervention. Studies have shown that pharmacist-acquired medication histories are more accurate than physician-acquired histories[12,15] and that pharmacy technicians are at least as accurate as pharmacists in performing this task, at a fraction of the cost.[16] In one study, transferring responsibility for medication reconciliation from medical residents to pharmacy technicians (under pharmacist supervision) was effective and well received by resident and staff physicians as well as by pharmacy technicians.[17] Therefore, developing a program for pharmacy technician–led medication reconciliation may represent the most reasonable approach to addressing the issues identified in the current study.

Our study had a number of limitations. First, we looked only at the completeness of admission medication reconciliation documentation and not the accuracy. We therefore were unable to quantify medication histories with incorrect doses or frequencies and did not capture whether home medications were omitted or ordered unintentionally. Second, it is possible that we overestimated the number of discrepancies that remained unclarified at discharge, because some may have been clarified verbally and correctly recorded on discharge prescriptions. Third, this chart review was completed by a single reviewer; although the outcomes themselves were not subjective, this might have been a source of bias.

The problem of poor documentation of asthma medication history is unlikely to be unique to our institution, and future quality improvement interventions are required. Studies conducted in other centres might yield different findings, especially if they have computerized physician order entry and forcing functions that require dose and frequency to be included for all medication orders. Although educational interventions have been of limited effectiveness,[6] certain individual centres have had success in reducing medication discrepancies by increasing the education of medical residents.[7,8,18] At our institution, increasing resident education to include the full and ongoing process of medication reconciliation, rather than just the technical aspects of completing a BPMH on a preprinted order form, may be of benefit. Mandating access to provincial electronic drug information systems for prescribers, as well as partnering with clinical pharmacists and pharmacy technicians at the time of admission, to facilitate communication with patients' community pharmacies, would result in more complete medication histories. In addition, patients and families must be educated about the importance of bringing an accurate medication list when accessing health care.

CONCLUSION

Documentation of inhaler medications on admission medication reconciliation forms prepared by resident physicians for pediatric asthma patients was often incomplete. Missing information about home asthma medications could negatively affect patient care and has potential to result in medication errors, adverse events, increased length of stay, and increased costs.

Future quality improvement interventions directed at the medication reconciliation process are required at the study institution, including increasing prescriber education and encouraging prescribers to access the provincial drug information system. Pharmacy services and resources, notably pharmacy technicians, have an important role to play in developing targeted solutions for this patient safety issue.

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Conflict between Pharmacy Preceptors and Pharmacy Learners in Experiential Education

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ABSTRACT

Background: The relationship between a preceptor and a learner is complex and can be prone to conflict. The issue of conflict in experiential education has been studied in medicine, nursing, social work, and education; however, conflict between pharmacy preceptors and learners has not been described.

Objective: To describe types of conflict between pharmacy preceptors and learners, the outcomes of such conflict, the impacts on the preceptor-learner relationship, and conflict-resolution strategies.

Methods: An anonymous electronic survey of pharmacist preceptors and pharmacy residents in British Columbia was conducted. The survey included various types of questions to enrich the quality of responses (e.g., Likert scale, ranking, and requests for comments). Descriptive statistics were used.

Results: Forty-nine participants completed the survey from the preceptor's perspective, 12 from the learner's perspective, and 4 from both perspectives. Sixty percent of preceptors (32/53) and 75% of learners (12/16) admitted experiencing conflict. Preceptors (n = 27) cited the learner's professionalism (74%), knowledge/skills (59%), communication issues (59%), personal issues (56%), and punctuality/attendance (52%) as causes of conflict. Learners, however (n = 12), cited differing expectations (67%), teaching versus learning style preferences (50%), and communication issues (67%) as causes of conflict. The majority of preceptors and learners indicated that conflict had negatively affected the relationship; however, most preceptors (69% [18/26]) and learners (50% [6/12]) agreed or strongly agreed with the statement, "I have generally felt comfortable working with preceptors/learners after a conflict." More learners than preceptors felt that the learner's ability to perform was negatively affected by the conflict (92% [11/12] versus 52% [13/25]). Preceptors were more likely to take initiative to resolve conflict. Verbal communication was the method of conflict resolution preferred by both preceptors and learners. Most preceptors and learners indicated that they felt that conflicts were generally resolved.

Conclusions: Conflict was common in the pharmacy preceptor-learner relationship. Pharmacy preceptors and learners had different perspectives about the causes and outcomes of conflict.

Keywords: conflict, education, pharmacy, preceptorship, teaching

RÉSUMÉ

Contexte : La relation entre le précepteur et l'apprenant est complexe et peut entraîner des conflits. Le problème du conflit dans le domaine de l'éducation expérientielle a été étudié en médecine, en infirmerie, en travail social et en éducation; cependant, il n'existe aucune description des conflits entre les précepteurs et les apprenants en pharmacie.

Objectif : Décrire les types de conflits entre les précepteurs en pharmacie et les apprenants, les conséquences de tels conflits ainsi que les impacts sur la relation précepteur-apprenant et les stratégies de résolution de conflit.

Méthodes : Une enquête électronique anonyme a été menée auprès de précepteurs et de résidents en pharmacie en Colombie-Britannique. L'enquête comprenait diverses questions visant à enrichir la qualité des réponses (p. ex., échelle de Likert, classement et demandes de commentaires). L'étude s'appuie sur des statistiques descriptives.

Résultats : Quarante-neuf participants ont répondu à l'enquête en adoptant le point de vue du précepteur, 12 en adoptant celui de l'apprenant et 4 ont adopté le point de vue de l'apprenant et du précepteur. Soixante pour cent des précepteurs (32/53) et 75 % des apprenants (12/16) ont admis traverser des conflits. Les sources de conflits citées par les précepteurs (n = 27) sont le professionnalisme de l'apprenant (74 %), les connaissances et compétences (59 %), les problèmes de communication (59 %), les problèmes personnels (56 %) ainsi que la ponctualité et la présence (52 %). Quant aux apprenants (n = 12), ils ont cité des attentes divergentes (67 %), des préférences de style d'enseignement ou d'apprentissage (50 %) et des problèmes de communication (67 %) comme causes de conflit. La majorité des précepteurs et des apprenants ont indiqué que ces conflits avaient affecté la relation; cependant, la plupart des précepteurs (69 % [18/26]) et des apprenants (50 % [6/12]) étaient d'accord ou fortement d'accord avec l'énoncé suivant : « En général, je me suis senti à l'aise de travailler avec des précepteurs ou des apprenants après un conflit. » Un plus grand nombre d'apprenants que de précepteurs ont perçu que le conflit avait perturbé la capacité de l'apprenant (92 % [11/12] par rapport à 52 % [13/25]). Les précepteurs étaient plus enclins à faire preuve d'initiative pour résoudre le conflit. La communication verbale était la méthode de résolution de conflit préférée des précepteurs et des apprenants. La plupart des précepteurs et des apprenants ont indiqué ressentir que les conflits étaient généralement résolus.

Conclusions : Le conflit était répandu dans la relation précepteur et apprenant en pharmacie. Les précepteurs en pharmacie et les apprenants avaient différents points de vue sur les causes et les conséquences de ces conflits.

Mots-clés : conflits, éducation, pharmacie, préceptorat, enseignement

INTRODUCTION

Experiential education plays a fundamental role in providing pharmacy learners with opportunities to acquire practical and clinical skills, and it assists in their transition to becoming health care professionals.[1,2] Experiential education often consists of rotations or practicums, during which learners apply the knowledge and skills learned in the classroom to actual patient care environments, under the supervision of their preceptors. The preceptor-learner relationship is an important aspect of the learner's experience and allows the learner to receive direct feedback to improve their practice and their readiness to become an independent practitioner.[2]

Both preceptors and learners may face challenges in their roles. Preceptors must balance their responsibilities to patient care and to their learners.[1] Learners are expected to apply knowledge and skills that they may or may not have been taught in the classroom. Learners must also assimilate into an unfamiliar environment and fulfill the expectations of the curriculum, as well as the expectations of the preceptor.[2,3] The practicum experience may be their first time applying knowledge in the clinical setting and receiving feedback from a preceptor. The learner and preceptor must collaborate, yet given the preceptor's responsibilities and the learner's desire for success, their relationship is not immune to conflict.[3]

Conflict may be a learning opportunity for both preceptor and learner, but failure to address unresolved conflict can lead to dissatisfaction for both parties and create an uncomfortable learning environment.[3] The preceptor-learner relationship has been described as a "significant, yet fragile liaison".[4] The issue of conflict in experiential education has been studied in medicine, nursing, social work, and education.[5] Conflict results from differences in preceptor and learner expectations, intergenerational disagreement, and personality clashes.[6,7] Conflict may facilitate or impede the learner's and/or preceptor's growth.[6] Communication and feedback are suggested methods of conflict resolution, with or without the use of a mediator.[3,6] Although preceptor-learner conflict has been studied in other health care disciplines, studies in pharmacy are lacking.[5,7] Given the potential impact of conflict on the learning environment and the overall outcome of the rotation, we thought it important to study preceptor-learner conflict in the pharmacy setting. The goal of this study was to explore the types of conflict that arise between pharmacy preceptors and pharmacy residents from their respective perspectives. The objectives were to describe the types of conflict that occur, the outcomes of such conflict, the impact of conflict on the preceptor-learner relationship, and the strategies used for resolution of conflict.

METHODS

We developed an anonymous electronic survey using FluidSurveys (complete survey presented in Appendix 1, available at https://cjhp.journals.publicknowledgeproject.org/index.php/cjhp/issue/view/202). A pharmacist and a pharmacy learner who were not involved in the study tested the survey before distribution. Intended participants were hospital pharmacist preceptors and pharmacy residents in British Columbia. There are 5 Accredited Canadian Pharmacy Residency programs in our province, all of which offer rotations across multiple hospitals. Because the study was open to preceptors of all types of pharmacy learners, we allowed pharmacy learners other than residents to complete the survey (and included their data in the analysis) as a way to enrich the perspective of the learner. The survey questions were devised to help answer the research team's main questions: What types of conflict are prevalent? What have been the outcomes of such conflict? How has conflict influenced overall relationships and practicum experiences? Questions relating to conflict outcomes were based on the survey by Mamchur and Myrick.[6] Participants had the option of completing the survey from the perspective of the preceptor, the perspective of the learner, or both (with current preceptors recalling their experiences as learners). Data provided by participants who answered from both perspectives were included in both analyses.

The survey used various methods of obtaining respondents' input, such as scaled questions, a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree), ranking, availability of a comments section, and open-ended questions to enrich the quality of the response. The survey was designed to take 10 to 20 minutes to complete. For all questions, responses were optional. For cases in which the participant did not answer all survey questions, responses were reported and analyzed as provided (i.e., total number of respondents for a given question was indicated in the results, and percentages were calculated accordingly). The analysis included data only from surveys in which the participant answered the question, "Have you ever experienced conflict with a preceptor or learner?" The survey did not provide a definition of "conflict", and participants were left to answer questions according to their own definitions of this concept.

One member of the study team (R.C.) contacted pharmacy coordinators, pharmacy practice residency coordinators, and pharmacy residents in the province via email distribution lists in August 2017. Coordinators were also asked to distribute the survey to preceptors and residents. We estimated that 450 pharmacy preceptors and 40 pharmacy residents could have participated in the survey. Participants were given 8 weeks to complete the survey. No reminders were sent, because we used distribution lists and did not have email addresses for all potential participants.

This study was based on a sample size of convenience. Descriptive statistics were used for data analysis. For open-ended questions, 3 reviewers (J.K., A.B., R.C.) grouped responses into themes. Where there was disagreement, the reviewers planned to discuss the themes and come to a consensus; however, there were no disagreements.

The study received ethics approval from the University of British Columbia – Children's and Women's Research Ethics Board.

RESULTS

Seventy-eight survey responses were received. Based on a total of 490 potential respondents, the response rate was 16%. Thirteen surveys were excluded because the respondents did not answer the question, "Have you ever experienced conflict with a preceptor or learner?" Therefore, 65 surveys were included in the analysis (Table 1). Of those included, 49 participants answered from the preceptor's perspective, 12 from the learner's perspective, and 4 from both perspectives. The majority of learners were pharmacy residents, and the majority of preceptors worked in the hospital setting. Preceptors (n = 53) indicated they had experience working in this role with pharmacy residents (83%), undergraduate pharmacy students (94%), entry-to-practice PharmD students (32%), and postbaccalaureate PharmD students (32%). Thirty-two preceptors (60%) and 12 learners (75%) reported having experienced conflict with a learner or a preceptor, respectively. The median percentage of relationships in which preceptors and learners had experienced conflict was 12.5% and 19.4%, respectively. None of the preceptors reported having had to withdraw from their role as a preceptor because of conflict with a learner; however, 17 (32%) of them reported that conflict with a learner had affected their willingness to serve as a preceptor for new learners in the future. The majority of preceptors indicated that they had experienced conflict with learners equally throughout their career (Table 2).

TABLE 1. Participant Characteristics

Characteristic	No. (%) of Participants (n = 65)	
Sex, female	45	(69)
Current pharmacy practice site	n = 63	
Hospital	58	(92)
Residential care	1	(2)
Ambulatory clinic	4	(6)
Current pharmacy learner program	n = 11	
Residency	8	(73)
Undergraduate pharmacy	1	(9)
PharmD	2	(18)
Learner experience	n = 16	
No. of practicums (median and range)	7.5	(2–24)
No. of preceptors (median and range)	9	(2–28)
Preceptor experience	n = 53	
No. of years as a preceptor (median and range)	6	(1–25)
No. of learners per year (median and range)	2	(1–20)

Types of Conflict

Participants identified a variety of issues that had led to preceptor-learner conflict in their relationships (Figure 1). Among preceptors, the most frequent causes of conflict and the most stressful causes of conflict were the learner's professionalism and the learner's knowledge/skills, and the learner's professionalism and the learner's personal issues were the most challenging to address (Table 3). In contrast, learners cited different expectations and differences in teaching versus learning styles as the most frequent causes of conflict, different expectations and personality conflict as the most stressful causes of conflict, and personality conflicts as the most challenging to address (Table 3). A greater proportion of preceptors reported having experienced the same type of conflict with multiple learners (58% [15/26]) than learners reported experiencing with multiple preceptors (25% [3/12]).

TABLE 2. Characteristics of Conflicts

Characteristic	Group; No. (%) of Participants[a]			
	Preceptors (n = 32)		Learners (n = 12)	
% of relationships with conflict (median and range)	12.5	(4.5–66.7)	19.4	(5.9–100)
When conflict has been experienced	n = 29		NA	
As a new preceptor	4	(14)		
As a veteran preceptor	4	(14)		
Equally throughout career	21	(72)		
Most frequent occurrence of conflict	n = 26		n = 12	
Daily	7	(27)	4	(33)
Weekly	13	(50)	4	(33)
Every few weeks	0	(0)	2	(17)
Once per rotation	6	(23)	2	(17)

[a]Except where indicated otherwise.

In response to an open-ended question asking participants to describe the worst conflict they had experienced, preceptors (n = 23) generally responded that these conflicts arose because of issues with the learner's professionalism, such as poor attitude, refusal to take initiative, unwillingness to participate in rotation activities, provision of inaccurate information to colleagues and patients, reluctance to accept suggestions/feedback, failure to meet deadlines, and poor attendance. Poor knowledge base or performance was less frequently cited. In response to the same question about the worst conflict they had experienced, learners (n = 10) responded that these conflicts had been due to differences in teaching versus learning style, a preceptor appearing disinterested or misjudging the learner, and lack of transparency

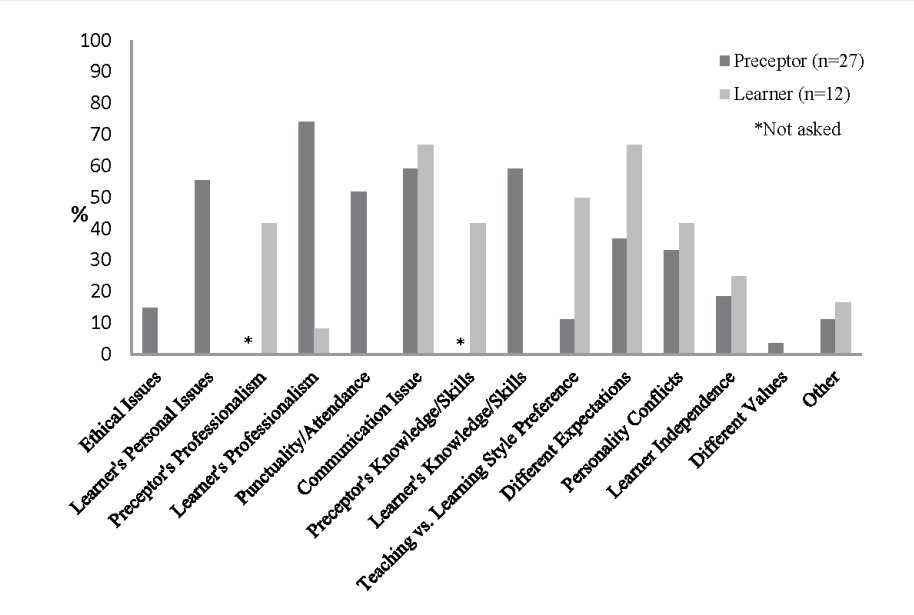

FIGURE 1. Causes of conflict between preceptors and learners.

TABLE 3. Causes of Conflict between Preceptors and Learners Reported as Most Frequent, Most Stressful, and Most Challenging to Address, Reported as Number (%) of Each Group

Issues	Most Frequent				Most Stressful				Most Challenging to Address			
	Preceptors (n = 27)		Learners (n = 12)		Preceptors (n = 27)		Learners (n = 12)		Preceptors (n = 27)		Learners (n = 12)	
Ethical issues	0		0		3	(11)	0		1	(4)	0	
Learner's personal issues	1	(4)	0		3	(11)	0		6	(22)	0	
Preceptor's professionalism[a]	–		1	(8)	–		0		–		2	(17)
Learner's professionalism	10	(37)	0		6	(22)	0		6	(22)	0	
Punctuality/attendance	2	(7)	0		2	(7)	0		1	(4)	0	
Communication issues	1	(4)	0		2	(7)	1	(8)	0		0	
Learner's knowledge/skills	7	(26)	1	(8)	4	(15)	2	(17)	4	(15)	1	(8)
Teaching versus learning style preference	0		3	(25)	0		1	(8)	0		1	(8)
Different expectations	3	(11)	5	(42)	3	(11)	3	(25)	3	(11)	1	(8)
Personality conflicts	1	(4)	0		2	(7)	3	(25)	3	(11)	4	(33)
Learner independence	0		0		0		0		2	(7)	1	(8)
Other	2	(7)	2	(17)	2	(7)	2	(17)	1	(4)	2	(17)

[a]Dash indicates that the question was not asked for this category of participant.

about progress or standing in the rotation. The conflict scenarios described had negative outcomes for the learner, the preceptor, or the relationship. Learners often described these most difficult conflicts as being unresolved.

Impact of Conflict on the Preceptor-Learner Relationship

When asked about the outcomes of conflicts, the majority of preceptors and learners indicated that there were negative effects on the relationship (Figure 2). At least half of preceptors (69%) and learners (50%) agreed or strongly agreed with the statement, "I have generally felt comfortable working with preceptors/learners after a conflict"; however, a larger proportion of learners than preceptors disagreed or strongly disagreed with this statement (25% versus 8%).

Outcomes of Conflict

Preceptors indicated that conflict had facilitated learner's growth, whereas learners indicated that conflict impeded their growth (Figure 2). Few preceptors and learners indicated that conflict had been detrimental to their image or had affected their personal health. More learners than preceptors agreed or strongly agreed with the statement, "I felt that the learner's/my ability to perform was negatively impacted by the conflict" (92% [11/12] versus 52% [13/25]). When asked what outcomes had arisen from the worst conflict, responses were similar to those in Figure 2, except that more preceptors and learners indicated that the learner's health had been compromised.

Conflict Resolution

More preceptors than learners reported that they "frequently" or "always" took initiative to resolve conflict (69% [18/26] versus 17% [2/12]). Forty-six percent (12/26) of preceptors agreed or strongly agreed with the statement, "I have generally felt comfortable addressing conflict with learners", whereas 35% (9/26) disagreed or strongly disagreed. Fifty percent (6/12) of learners agreed or strongly agreed with the statement, "I generally felt comfortable with the way preceptors addressed conflict with me", and 17% (2/12) disagreed or strongly disagreed. When learners were asked about resolving conflict, 67% (8/12) agreed or strongly agreed with the statement, "It is better to just 'grin and bear it' when conflict arises."

With respect to methods used to resolve conflict, as reported by 26 preceptors, the majority of preceptors reported having used verbal communication (100%) or having involved another pharmacist/preceptor (65%) or the program facilitator/mediator (54%). Fewer of these preceptors reported using written communication (27%) or involving

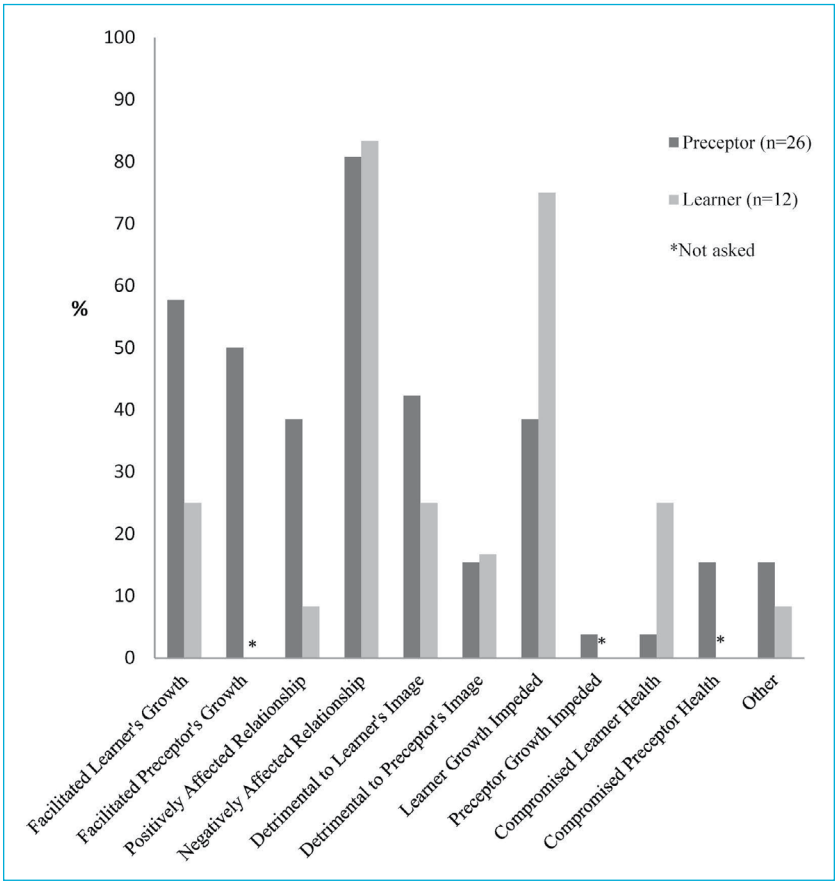

FIGURE 2. Outcomes of conflict between preceptors and learners.

their supervisor (35%) or the program director/coordinator (38%). Preceptors found verbal communication to be the most effective strategy (65% [17/26), and learners were most comfortable with this method (58% [7/12]). Preceptors and learners also cited involving another pharmacist or a program facilitator or director as a preferred method for conflict resolution. Large proportions of preceptors (n = 26) and learners (n = 12) indicated their perception that conflicts were resolved either frequently (42% in both groups) or sometimes (54% and 50%, respectively).

DISCUSSION

In this survey study, large proportions of preceptors and learners reported ever having experienced conflict; however, conflict occurred in less than 20% of relationships. In contrast, Mamchur and Myrick[6] surveyed preceptors and learners from medicine, nursing, social work, and education and found that 25% of preceptors and 32% of learners reported ever experiencing conflicts in their relationships. The prevalence ranged from 17% to 50% depending on the profession and the perspective of learner versus preceptor in that study; both preceptors and learners in family medicine reported the highest incidence of conflict.[6] The higher prevalence in our study may be due to preceptors and learners who had experienced conflict being more likely to participate in the survey or may be related to differences between professions.

Mamchur and Myrick[6] found that the majority of learners listed expectations of the preceptor and personal/personality issues with the preceptor as causes of conflict, whereas preceptors listed expectations of the preceptor, expectations of the student, student knowledge, and student skill as causes of conflict. In other qualitative studies about preceptor-learner conflict, participants described personality conflict, different expectations, knowledge, and skills as themes causing conflict.[5,7] Reported disparities between preceptors' and learners' perceptions about the causes of conflict are common regardless of the health care profession.[5-7] In our study, we also found disparity between preceptors' and learners' perceptions of causes of conflict, as well as what they reported to be the most frequent, stressful, and difficult to address causes of conflict. In our survey, we did not define conflict for the respondent; therefore, preceptors and learners might have had different perspectives of what constitutes conflict. Additionally, preceptors and learners may have different perspectives on their respective roles in conflict. The majority of preceptors and learners reported communication issues as a cause of conflict. Learners reported issues with different expectations and differences in teaching versus learning styles causing conflict. Professionalism was described by preceptors as one of the most frequent and most stressful causes of conflict and the most difficult type of conflict to address. This may relate to difficulty in defining what specific behaviours are to be evaluated within "professionalism" or, possibly, to pharmacists having heightened awareness because of attention to professionalism in pharmacy curricula in recent years.[8] Professionalism, like conflict, can be difficult to define, as there is little consensus in the literature.[9] The Canadian Pharmacy Residency Board, for example, requires pharmacy residents to hold high professional ideals, such as being committed to continued learning and improvement, using constructive feedback, exhibiting professional behaviours and relationships, and demonstrating a commitment to excellence.[10]

Similar to what was reported by Mamchur and Myrick,[6] preceptors in our study had a more positive outlook on the outcomes of conflict than did learners. It is possible that preceptors recognize conflict as an important learning experience, whereas learners view it as detrimental to their learning and self-esteem, and fail to see the value of practising conflict resolution. The real or perceived power differential between preceptor and learner may also play a role, including fears of negative consequences. This may relate to our findings that few learners reported taking the initiative to resolve conflict and more than two-thirds of learners agreed with the statement that it is better to just "grin and bear it" when conflict arises. These results concurred with those of Myrick and others,[5] who surveyed learners in the disciplines of medicine, nursing, social work, and education in relation to preceptor-learner conflict. Many participants in that study stated that they felt the best course of action was to remain silent, rather than to make attempts at resolution of conflict. Being able to resolve conflict in a respectful manner and being able to provide effective and constructive feedback are aspects of professionalism.[8]

Most participants in our study reported the perception that conflicts were frequently or sometimes resolved, which is similar to findings for other professions.[6] Although both preceptors and learners indicated that conflict negatively affected the relationship, both groups generally felt comfortable working with one another afterward. Our use of mostly closed-ended questions did not allow us to explore the relationship between the extent to which conflict was addressed and resolved and the impact on the preceptor-learner relationship. In response to our open-ended question asking participants to describe the worst conflict they had experienced, the learners' narratives often described the conflict as both having a negative outcome and being unresolved.

Given the prevalence of conflict and the potential negative outcomes in preceptor-learner relationships, increasing awareness and incorporating conflict-resolution training would be important for both preceptors and learners. Some preceptor training programs incorporate case-based scenarios or discussions to address conflict resolution.[3,11] Emotionally intelligent behaviours, such as reflection, reframing, controlling discomfort, and expressing emotions appropriately, have been described by pharmacy and nursing students as helpful in managing conflict during clinical placements.[12]

With most learners being reluctant to address conflict and their perceptions of the causes of conflict being different from those of preceptors, it is possible that many conflicts go unnoticed by preceptors. Given that conflict resolution is an aspect of professionalism, developing skills in conflict resolution through both didactic and experiential learning may be helpful for learners. Increasing awareness of learners' perceptions of conflict may allow preceptors to assist learners in addressing and resolving conflict.

The main limitation of this study was the low response rate. We estimated that up to 450 hospital-based pharmacist preceptors and 40 pharmacy residents could have responded to our survey; however, the exact number of potential participants who received the invitation to participate in the study is unknown. There may have been selection bias, with preceptors and learners who experienced conflict being more likely to respond to the survey. We also focused on hospital-based programs, so our findings may not reflect the experiences of preceptors and learners in community or ambulatory-based programs. Given the nature of our study design, we were unable to explore specific conflicts that occur within a preceptor-learner relationship or how conflict changes over time.

CONCLUSION

Conflict within the pharmacy preceptor-learner relationship was common among participants in our survey; however, preceptors and learners had different perspectives about the causes of conflict. Learners frequently reported that conflict had negative outcomes, whereas preceptors identified that professional growth and skill development can result from conflict. Preceptors indicated that they took the initiative to resolve conflict but were not necessarily comfortable doing so.

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Identification of Staphylococci by Polymerase Chain Reaction Directly from a Positive Blood Culture and Effect on Patient Care

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ABSTRACT

Background: As one of the most common bloodstream infections worldwide, *Staphylococcus aureus* bacteremia places a major burden on health care. Implementation of a rapid, genetic-based diagnostic test may have important implications in the clinical management of patients with *S. aureus* bacteremia.

Objectives: The primary objective was to assess concordance between testing based on polymerase chain reaction (PCR) and the current gold standard, culture and sensitivity testing; the secondary objective was to assess the impact of this technology on patient care.

Methods: A pre–post intervention retrospective chart review was used to document the hospital course of patients with a diagnosis of *S. aureus* bacteremia before and after implementation of the PCR-based diagnostic system. Laboratory results from all patient samples subjected to PCR-based analysis following implementation of this system were compared with culture and sensitivity data for the same samples to determine accuracy of the new system. In addition, time to optimal therapy for each patient was calculated as the interval between the initiation of empiric and terminal therapies. The appropriateness of antimicrobial treatment was characterized as guideline-concordant, nonconcordant with the guidelines, or nonconcordant yet still clinically appropriate.

Results: In total, 98 and 99 patients met the inclusion criteria before and after implementation of the PCR-based diagnostic system, respectively. PCR-based results displayed 99.8% concordance (440/441 total samples) with results from culture and sensitivity testing. The time to optimal therapy was significantly shorter after implementation, by a mean of 22.8 h ($p < 0.001$). Overall, 97% of empiric and 99% of terminal antimicrobial regimens were either guideline-concordant or clinically appropriate for treatment of *S. aureus* bacteremia; 3% of empiric and 1% of terminal antimicrobial regimens were nonconcordant with clinical guidelines without any explanation based on other clinical considerations.

Conclusions: The study findings support the utility of using a direct-from-positive-blood-culture PCR-based diagnostic tool as the primary method of identifying *S. aureus* bacteremia in patients, as well as the acceptance of and acting upon the new assay's results by our local clinicians. PCR-based assays can help reduce the time to optimal terminal therapy for patients with bacteremia.

Keywords: bacteremia, antimicrobial stewardship, polymerase chain reaction, diagnostic testing, GeneXpert

RÉSUMÉ

Contexte : La bactériémie à *Staphylococcus aureus* (BAC-SA), qui est l'une des infections du sang les plus répandues dans le monde, fait peser une lourde charge sur les soins de santé. La mise en place d'un test diagnostique génétique rapide pourrait avoir des retombées importantes sur la gestion clinique des patients présentant une BAC-SA.

Objectifs : L'objectif principal consistait à évaluer la concordance entre les tests basés sur la réaction en chaîne par polymérase (PCR) et le test de sensibilité et de culture, qui est la référence absolue actuelle; l'objectif secondaire consistait à évaluer l'impact de cette technologie sur les soins des patients.

Méthodes : Un examen rétrospectif des dossiers pré- et post-intervention a servi à décrire le séjour à l'hôpital des patients ayant reçu un diagnostic de BAC-SA avant et après la mise en place du système de diagnostic de la PCR. Les résultats de laboratoire de tous les échantillons des patients soumis à une analyse de la PCR à la suite de la mise en place de ce système ont été comparés avec les données relatives à la culture et à la sensibilité de ces mêmes échantillons afin de déterminer la précision du nouveau système. De plus, l'évaluation du délai d'atteinte du traitement optimal de chaque patient repose sur le calcul de l'intervalle entre le début des thérapies empiriques et terminales. La pertinence du traitement antimicrobien était caractérisée comme suit : concordance avec les lignes directrices, non-concordance avec les lignes directrices ou non-concordance mais encore approprié d'un point de vue clinique.

Résultats : Au total, 98 et 99 patients ont satisfait au critère d'inclusion respectivement avant et après la mise en place du système de diagnostic de la PCR. Les résultats basés sur la PCR affichaient une concordance de 99,8 % (440/441 échantillons au total) avec les résultats des tests de sensibilité et de culture. La diminution du délai d'atteinte du traitement optimal était importante après la mise en place du système, puisqu'elle atteignait en moyenne 22,8 h ($p < 0,001$). De manière générale, 97 % des régimes antimicrobiens empiriques et 99 % des régimes antimicrobiens terminaux concordaient avec les lignes directrices ou étaient cliniquement appropriés pour le traitement de la BAC-SA; 3 % des régimes antimicrobiens empiriques et 1 % des régimes antimicrobiens terminaux n'étaient pas conformes aux lignes directrices cliniques sans qu'aucune explication basée sur d'autres considérations cliniques n'ait été donnée.

Conclusions : Les résultats de l'étude confirment la nécessité d'utiliser un outil diagnostique basé sur la PCR directement de l'hémoculture positive en guise de méthode principale pour déterminer la présence de BAC-SA chez les patients ainsi que l'acceptation et l'utilisation des nouveaux résultats du test par nos cliniciens locaux. Les tests basés sur la PCR peuvent aider à réduire le délai d'attente du traitement optimal pour les patients atteints de BAC-SA.

Mots-clés : bactériémie, gestion de l'utilisation des antimicrobiens, réaction en chaîne par polymérase, test de diagnostic, GeneXpert

INTRODUCTION

As one of the most common bloodstream infections worldwide, *Staphylococcus aureus* bacteremia places a major burden on health care.[1] Despite existing as a commensal on the skin and in the nares, *S. aureus* in the bloodstream can result in an invasive disease, contributing to clinical illness and notoriously high mortality rates.[2] With the current prevalence of methicillin-resistant *S. aureus* (MRSA) above 20% in the Regina area (unpublished laboratory data), individuals suspected of having *S. aureus* bacteremia are typically started on empiric therapy with broad-spectrum antibiotics to cover both MRSA and methicillin-susceptible *S. aureus* (MSSA) until microorganisms are identified and susceptibilities are available. Using conventional methods, it may take 48 h or longer to identify the microorganism and perform susceptibility testing after a positive blood culture result has been obtained.[3,4] Not only does this lag period contribute to the potential for drug toxicities and antimicrobial resistance, but the length of time to optimal therapy has been shown to directly influence infection-related mortality and length of stay.[2,5]

In 2018, the Saskatchewan Health Authority – Regina Area began to employ a new method for identifying *S. aureus* bacteremia. Using the GeneXpert IV system, the Xpert MRSA/SA BC assay (Cepheid) allows identification of MRSA and MSSA using material obtained directly from a blood culture sample when gram-positive cocci in clusters have been identified. This system uses real-time polymerase chain reaction (PCR) to amplify and detect 3 distinct staphylococci genes: the gene for staphylococcal protein A (*spa*), which verifies the identity of *S. aureus;* a specific junction of the staphylococcal cassette chromosome (*SCCmec*); and the *mecA* gene for methicillin resistance. The detection of all 3 genes indicates an MRSA-positive sample, whereas the detection of *spa* alone or in conjunction with *SCCmec* indicates MSSA, and the absence of *spa* indicates other gram-positive cocci (for example, coagulase-negative staphylococci or micrococci).[6] The GeneXpert system has the potential to allow clinicians to identify MRSA/MSSA from positive blood culture samples in under 1 h.[7]

Relative to traditional culture and sensitivity testing, the GeneXpert system has been shown to identify bacterial strains with high sensitivity and specificity, dramatically reduce time to optimal antibiotic therapy, and reduce overall use of empiric agents.[8,9] The limit of detection has been reported as 600 colony-forming units (CFU)/mL for *S. aureus* and 800 CFU/mL for MRSA, comparable to direct culture methods but substantially higher than enrichment cultures used in laboratory settings.[10,11] In the case of samples containing mixed bacterial species in quantities near the limit of detection, the risk of false or variable results increases; however, compared with reference culture, the sensitivity of GeneXpert for 792 specimens was reported as 98.1% for MRSA-positive samples, 99.6% for MRSA-negative samples, 99.6% for *S. aureus*–positive samples, and 99.5% for specimens negative for *S. aureus*. Additionally, testing of 101 different gram-positive, gram-negative, and yeast strains revealed 100% analytical specificity in which all results were reported as MRSA-negative and *S. aureus*–negative by the GeneXpert assay.[10]

Although substantial evidence has shown the utility of PCR-based assays, few researchers have investigated their influence on patient care. We evaluated the patient care process from initial presentation to the emergency department to terminal antimicrobial treatment (Figure 1). The primary objective was to assess the accuracy of the GeneXpert system relative to the current gold standard of culture and sensitivity testing, and the secondary objective was to assess the impact of the GeneXpert system on patient care.

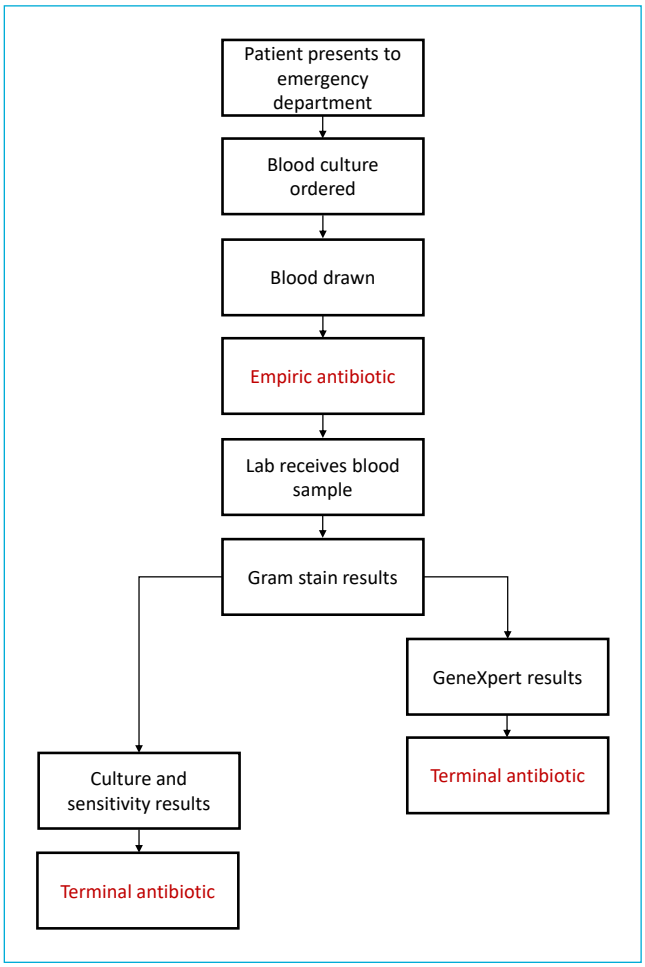

FIGURE 1. The flow of care for patients with a diagnosis of *Staphylococcus aureus* bacteremia. After presentation to the emergency department, blood culture was ordered for patients with suspected bacteremia. Blood samples were drawn before initiation of an empiric antibiotic, sent to the laboratory, and subjected to Gram staining. Each patient's terminal antimicrobial therapy was initiated either after culture and sensitivity testing (pre-implementation group) or after receipt of GeneXpert results (post-implementation group).

METHODS

This pre–post intervention retrospective cohort chart review involved patients in the Saskatchewan Health Authority – Regina Area admitted to either the Regina General Hospital or Pasqua Hospital or treated as outpatients in the emergency department of either hospital. The study population included patients 18 years of age or older who received treatment for *S. aureus* bacteremia. Admitted patients and emergency outpatients identified as having gram-positive cocci in clusters based on Gram staining of a cultured blood sample between October 17, 2017, and April 11, 2018 (pre-implementation of the GeneXpert system) and between April 12, 2018, and June 2, 2019 (post-implementation) were eligible for inclusion. Patients receiving outpatient hemodialysis were excluded because of the inaccessibility of their medical files. Randomly selected convenience samples of 99 patients before implementation and 98 patients after implementation were included.

Data for the following variables were collected: demographic and clinical characteristics (age, Sequential Organ Failure Assessment [SOFA] score,[12] Acute Physiology and Chronic Health Evaluation [APACHE] II score,[13] Charlson Comorbidity Index,[14] MRSA risk factors [IV drug use, MRSA history, positive MRSA screening result, hospital admission or antimicrobial use in the past 90 days, overcrowded living conditions, chronic illnesses, indwelling devices or prostheses],[15] primary source of infection,[16] most responsible admission diagnosis, length of stay, discharge disposition, date and time of presentation to the emergency department, date and time of triage), blood culture information (date and time that blood cultures were ordered and samples were drawn and received by the laboratory, as well as date and time of reported results from Gram staining, GeneXpert analysis, and culture and sensitivity testing), and information on antimicrobial use (date and time of empiric and terminal antibiotic therapy, as well as appropriateness). An unpaired *t* test was used to identify statistically significant differences between the pre- and post-implementation groups in terms of mean age, length of stay, SOFA score, APACHE II score, Charlson comorbidity index, and time to optimal therapy. Categorical data (e.g., discharge disposition) were compared with a χ^2 test. All information was captured using the online Research Electronic Database Capture (REDCap) tool.[17,18]

Notification of laboratory results was the same before and after implementation, whereby positive Gram stain results were immediately conveyed by telephone to the ordering ward, and organism identification and susceptibility reports were made available in the electronic health record. Laboratory results from all patient samples subjected to GeneXpert analysis (April 12, 2018, to June 2, 2019) were compared with corresponding culture and sensitivity data to determine concordance between methods.

The date and time of antimicrobial therapy were determined from administration times documented in the medication administration record of the patient's medical chart. Empiric and terminal therapies were recorded as the first occurrence of the respective antimicrobials in the medication administration record. If antimicrobial therapy was terminated after laboratory results became available (e.g., if only 1 of 4 culture bottles had a positive result for gram-positive cocci and was ruled a contaminant), the date and time of terminal therapy was considered to be the final dose of empiric therapy documented in the medication administration record. If a patient remained on empiric therapy (e.g., tested positive for MRSA), terminal therapy was recorded as the date and time that either culture and sensitivity results became available (before implementation of the GeneXpert system) or GeneXpert results became available (after implementation). For each patient, time to optimal therapy was calculated as the interval between the initiation of empiric and terminal therapies and plotted on a control chart (X chart; QI Macros, KnowWhere International) for analysis of change signals in the data.

The appropriateness of antimicrobial treatment was characterized as guideline-concordant, nonconcordant, or nonconcordant yet still clinically appropriate.[19] Guideline concordance was defined as the use of vancomycin, linezolid, or daptomycin as empiric therapy for patients with positive blood culture results and as terminal therapy for patients with MRSA; cloxacillin or cefazolin as terminal therapy for MSSA; and either discontinuation of antibiotic therapy or use of an optimal narrow-spectrum agent for other gram-positive cocci identified. Empiric treatment with cloxacillin or cefazolin for patients without other risk factors for MRSA (e.g., those with young age, few comorbidities, no previous hospital admissions or antimicrobial use) was considered guideline-nonconcordant yet clinically appropriate. Nonconcordance was defined as the use of sulfamethoxazole-trimethoprim for MRSA and empiric agents such as piperacillin-tazobactam, ertapenem, meropenem, or ceftriaxone for MRSA-negative infections in the absence of other risk factors or infections in other body sites. For cases in which therapy was deemed nonconcordant, a clinical pharmacist (J.F.M. or C.P.) reviewed patient comorbidities, the clinical picture, and MRSA risk factors to assess whether the treatment was clinically appropriate. For example, prolonged, broader-spectrum empiric treatment of patients with multiple comorbidities or sources of infection, despite narrower-spectrum therapies being available, would be considered nonconcordant yet clinically appropriate antimicrobial use.

This study was exempted from ethical review by the former Regina Qu'Appelle Health Region (RQHR) Research Ethics Board (REB-19-62) and was conducted in accordance with the ethical standards of the former RQHR Research Ethics Board, the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, and the Helsinki Declaration.

RESULTS

Patient Characteristics

Of the 263 charts reviewed, 66 were excluded because the patients were not treated for *S. aureus* bacteremia (left against medical advice, discharged before antibiotic administration, or not receiving any antimicrobial therapy because a positive culture result was ruled as representing a contaminant), because they did not receive an initial antibiotic before blood culture results became available, or because blood culture samples were not tested by the GeneXpert system in the post-implementation phase. Patient demographic characteristics in the 2 groups are presented in Table 1. There were no significant differences between groups in average age, disposition, length of stay, SOFA score, APACHE II score, or Charlson comorbidity index.

Laboratory Results

The ratio of MRSA to MSSA to other gram-positive cocci was similar before implementation of the GeneXpert system (17:38:44) and after implementation (14:26:58).

Concordance with Culture and Sensitivity Testing

For all samples tested, the GeneXpert system displayed 99.8% concordance (440/441) relative to culture and sensitivity testing. The assay falsely identified 1 sample as MRSA-positive, whereas further susceptibility testing showed that it was MSSA-positive.

Time to Optimal Therapy

From the time of initial blood sampling, the mean intervals to reported Gram staining results, GeneXpert results, and final culture and sensitivity results were 23.1 h, 26.4 h, and 100.6 h, respectively. A statistically significant difference was found in the time to optimal therapy between groups: mean time 63.6 (standard deviation [SD] 122.4) h before implementation of the GeneXpert system and 40.8 (SD 68.5) h after implementation, a difference of 22.8 h ($p < 0.001$). The control chart analysis did not reveal any special-cause variation in the time to optimal antimicrobial therapy. However, a decrease in the upper 3-σ control limit was observed for patients treated after implementation of the GeneXpert system, which indicates less variability in the data points and more frequent observation of shorter lengths of time to optimal therapy relative to the pre-intervention group (Figure 2).

Antimicrobials

For the pre- and post-implementation groups combined, 97% (191/197) of empiric regimens and 99% (198/200) of terminal antimicrobial therapies were either guideline-concordant or clinically appropriate for the treatment of *S. aureus* bacteremia. Conversely, 3% (6/197) of empiric regimens and 1% (2/200) of terminal antimicrobial therapies were nonconcordant with clinical guidelines without any explanation based on other clinical considerations.

DISCUSSION

The utility of rapid PCR-based assays in the treatment of *S. aureus* bacteremia has been increasingly recognized in the past decade.[20] When the clinical role of a tool such as the GeneXpert system is being considered, speed and accuracy are key determinants, in addition to cost, influence on workflow, and laboratory implementation. As a quality control measure, we compared the concordance between the GeneXpert system and culture and sensitivity results from the same

TABLE 1. Characteristics of Cohorts before and after Implementation of the GeneXpert System

Variable	Cohort; Mean Value or No. of Patients		Statistical Test Results
	Before GeneXpert (n = 99)	After GeneXpert (n = 98)	
Demographic and clinical characteristics (means)			
Age (years)	56.7	56.3	$t = 0.1429$ ($p = 0.89$)
Length of stay (days)	21.16	20.35	$t = 0.2229$ ($p = 0.82$)
APACHE II	14.0	16.0	$t = 1.6606$ ($p = 0.10$)
SOFA	4.1	4.3	$t = 0.5121$ ($p = 0.61$)
CCI	3.5	4.1	$t = 1.2072$ ($p = 0.23$)
Discharge disposition			
No. deceased	8	15	$\chi^2 = 2.496$ ($p = 0.29$)
No. discharged home	65	59	
No. discharged to long-term care	26	24	
Drug therapy			
No. (%) requiring change from empiric to narrow-spectrum therapy	82 (83)	84 (86)	$\chi^2 = 0.337$ ($p = 0.56$)

APACHE = Acute Physiology and Chronic Health Evaluation, CCI = Charlson Comorbidity Index, SOFA = Sequential Organ Failure Assessment.

blood samples with positive Gram staining results. Among 441 samples, only 1 instance of discordance was observed over a period of approximately 5 months after implementation. In that case, the causative organism was identified as MRSA by the GeneXpert system but displayed cloxacillin sensitivity; the culture and sensitivity results were regarded as the gold standard and were used to facilitate patient treatment. The risk of false-positive and false-negative test results is one limitation associated with the use of molecular assays. False detection of *mecA* in an empty staphylococcal cassette chromosome is a predominant cause of false positives, whereas borderline oxacillin resistance, resistance through alternative mechanisms (altered penicillin binding proteins), or the presence of the *mecA* homologue *mecC* contribute to false-negative results.[10,21] Through distinct detection of *mecA* in addition to *SCCmec* and *spa*, the primers and probes of the GeneXpert system minimize the prevalence of false detection relative to other assays; however, this technology should continue to be re-evaluated as new bacterial variants emerge.[6,22]

The greater speed of detection of the GeneXpert system relative to conventional culture and sensitivity testing remains uncontested, yet the implications of this speed for patient care remain poorly defined. We evaluated the influence of the GeneXpert system on time to optimal antibiotic therapy. Because there were no statistically significant differences in age, SOFA score, APACHE II score, or Charlson comorbidity index between the patient groups, any significant differences in the study variables were attributed to use of the GeneXpert system. We found a significant reduction in the mean time to optimal therapy after implementation of the GeneXpert system, by 22.8 h. This indicates acceptance of diagnostic results from the new system by local clinicians and subsequent changes to antimicrobial therapy for patients. The importance of earlier microbiology results and shorter time to optimal treatment has been reported in numerous studies. For example, in their retrospective trial, Lodise and others[5] found that delayed treatment was an independent predictor of infection-related mortality in patients with *S. aureus* bacteremia, whereas another retrospective study examining 684 cases of *S. aureus* bacteremia concluded that patients with the longest time to blood culture positivity had a 30-day mortality rate of 39%, compared with 17% for those with early detection.[23] Our study was relatively small, and we did not observe any difference in mortality between groups; this may be an avenue for future research.

In terms of cost (where all costs are reported in Canadian dollars, unless otherwise noted, and are relevant to the date of reporting and the respective currency), workflow, and practicality of laboratory implementation, the feasibility of integrating the GeneXpert system into tertiary care is an important consideration. In 2010, the list prices for the PCR test and GeneXpert IV system were $65 USD and $35 000 USD, respectively.[24] Total implementation costs at our centre were estimated at $33 320.60 per year, excluding the price of the GeneXpert instrumentation, which was already being utilized by our microbiology laboratory for other testing. Implementation costs included monthly quality control ($819.60 per year), annual proficiency testing ($400 per year), and the cost of patient testing based on the number of positive blood culture results in 2016 ($68.30 per patient for 470 patients with positive blood culture results, for a total estimated cost of $32 101 per year). We did not directly evaluate

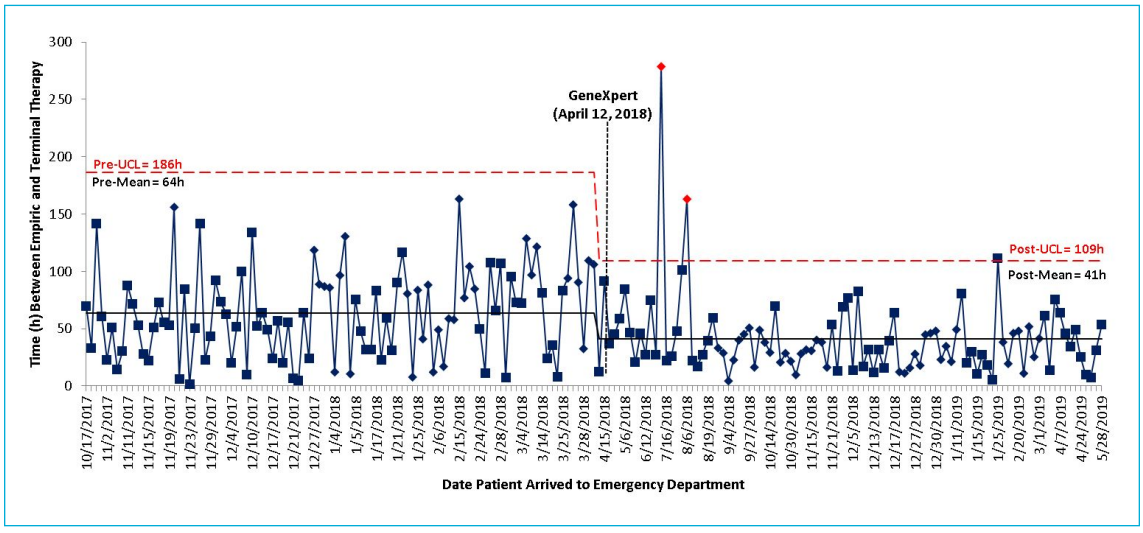

FIGURE 2. Time (h) between administration of empiric and terminal therapy before (October 17, 2017, to April 11, 2018) and after (April 12, 2018, to June 2, 2019) implementation of the GeneXpert system, which occurred on April 12, 2018 (black dashed line). Data from patients in the post-implementation group showed a decrease in the upper 3-σ control limit (UCL, red dashed line), indicating less variability in the data, and a reduction in the mean time to optimal terminal therapy (solid black line). These results suggest that the GeneXpert system allowed initiation of optimal terminal therapy in a shorter period of time and more consistently, relative to patients in the pre-implementation group.

the potential cost savings associated with empiric antimicrobial usage before and after implementation of the GeneXpert system; however, a 10-day course of vancomycin is more expensive ($234–$856) than cloxacillin ($72–$134), cephalexin ($30–$50), and other narrow-spectrum antimicrobials.[25] Previous studies have shown little difference in hospital costs accrued during the days of antimicrobial therapy with GeneXpert system use; however, one study demonstrated that mean hospital costs were $21 387 USD less, over a 4-month period, after implementation because of fewer patient-days spent in the intensive care unit (ICU) and reduced length of hospital stay.[24] Similarly, GeneXpert technology was found to reduce the number of ICU isolation days by 44% relative to conventional culture methods, with an estimated cost savings of €121.76 per isolation day avoided.[26,27]

Despite the 20% rate of MRSA in our area, most patients (166/197) were identified as having infection with MSSA or infection caused by other gram-positive cocci. The high incidence of non–*S. aureus* infections (102/197) may be attributed to the clinical prevalence of coagulase-negative staphylococci. This group of organisms has become a major cause of nosocomial infection and, in addition to *S. aureus*, represents one of the most common blood culture isolates, whether due to true infection or contamination from the skin surface.[28] From an antimicrobial stewardship standpoint, being able to rule out MRSA sooner in these patients may limit the use of empiric agents such as vancomycin, reducing the potential for adverse drug events and the development of resistant organisms such as vancomycin-resistant enterococci or vancomycin-resistant *S. aureus*.[8,15,26] Additionally, earlier access to MRSA-negative results may enable practitioners to discharge patients to home with IV antimicrobial therapy and avoid calling them back for treatment once laboratory results are available, thereby decreasing the utilization of downstream resources. For the 31 patients with positive results for MRSA, the delay in confirmation of presence of this organism likely had little effect on outcomes, because empiric coverage with an antimicrobial having MRSA activity (such as vancomycin) is standard in the tertiary centres participating in this study. Faster identification of MRSA may have more utility in centres with lower community rates of MRSA, which do not typically initiate vancomycin for *S. aureus* bacteremia, enabling faster coverage and an increased potential for beneficial patient outcomes.[29]

The control chart (Figure 2) did not reveal any special-cause variation in the data. It was anticipated that there might be a downward shift (i.e., a reduction in the length of time to optimal therapy) after implementation of the GeneXpert system; however, inherent variability in individual data points resulted in lack of an obvious trend. We did observe a drop in overall mean time to optimal therapy. After implementation of the GeneXpert system, there was less variability in time to optimal therapy as the data points produced a smaller upper 3-σ control limit. This suggests that clinicians were more consistently able to provide optimal terminal antibiotic therapy sooner following implementation of the GeneXpert system.

There was no significant difference in length of stay between the pre- and post-implementation groups. One of the earlier studies of this platform, conducted by Bauer and others[24] and published in 2010, demonstrated the power of this tool to reduce patient length of stay by 6.2 days on average, a difference that was associated with a noticeable cost reduction because patients spent less time in the ICU. The difference in outcomes between studies may be attributed to the study populations, given that the majority of patients in the earlier study were from the ICU (66% pre- and 67% post-implementation), whereas our population consisted largely of emergency outpatients. Additional factors may include advances in medical care over time, given that the studies were conducted nearly a decade apart, or the previously mentioned inherent variability in patient data resulting in no significant difference in patient length of stay between our groups.

The clinical management of *S. aureus* bacteremia was found to be acceptable, as nearly all antimicrobial regimens were either concordant with guidelines or nonconcordant but still clinically appropriate. There did appear to be a lag associated with terminal antibiotic administration, even with use of the GeneXpert system: on average, results were available within 26.4 h, yet mean time to optimal terminal therapy was 40.8 h. This delay may have been influenced by factors such as clinical decision-making, dosing intervals for antimicrobial drugs, or potential discrepancies in charting or record keeping in relation to the time of actual drug administration; therefore, it is difficult to pinpoint clinical interventions that might shorten this time frame.

The limitations of this study include the retrospective nature of chart reviews, which has been described as increasing susceptibility to bias in data selection and leading to greater difficulty in establishing causal relationships than prospective studies.[30] Additionally, this was a relatively small, single-centre study. With more data, we might see a more significant difference in variables, such as discharge disposition. The strengths of this study include the random selection of patients from a relatively large pool, which reduces the potential for selection bias, as well as the combination of analyses for quality improvement and parametric and nonparametric statistical methods. This approach allowed us to analyze data from individual samples to identify trends, as well as to compare means between groups.

CONCLUSION

The implementation of a new, rapid diagnostic technology for the identification of *S. aureus* bacteremia is a practical step in the clinical management of patients. The GeneXpert system displayed a high level of concordance with the results of conventional culture and sensitivity testing and significantly

decreased the time to initiation of terminal antimicrobial therapy. PCR-based assays play an important role at the frontier of antimicrobial stewardship by enabling faster diagnosis and a reduction in the use of broad-spectrum agents, which may help combat previously reported high mortality rates associated with *S. aureus* bacteremia and the progression of antimicrobial resistance.

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Patient Factors Associated with Prescribing of Iron for IV Administration: A Descriptive Study

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ABSTRACT

Background: IV administration of iron is appropriate for the treatment of iron deficiency anemia (IDA) when orally administered iron has not been effective, tolerated, or clinically appropriate. In Calgary, Alberta, high levels of IV iron utilization required review, because of significant health care resource utilization, high cost, and reduced accessibility.

Objectives: The primary objective was to describe the population of adult patients in Calgary with estimated glomerular filtration rate greater than or equal to 30 mL/min/1.73 m^2 for whom IV iron was dispensed from acute care facilities, in terms of pretreatment laboratory data, previous use of oral iron, and treatment location, as well as to characterize dose and product selection for IV iron. The secondary objective was to determine the proportion of inpatients whose treatment was in alignment with the Toward Optimized Practice clinical practice guideline for IDA.

Methods: A retrospective review of electronic charts was used to obtain data about patients with a first dose of IV iron dispensed in Calgary hospitals between March 1 and December 31, 2018. The data were analyzed descriptively.

Results: A total of 1352 patients met the inclusion criteria. These patients received a total of 3532 doses of IV iron, 97.1% of which were iron sucrose, at a median of 300 mg per infusion. Laboratory indices assessed before the first infusion were hemoglobin (mean 92, standard deviation [SD] 19.6 g/L), mean corpuscular volume (mean 81 [SD 10.3] fL), and ferritin (median 18 [interquartile range 9–48] µg/L). Among the included patients, 233 (17.2%) had oral iron dispensed within 90 days before their first IV dose of iron. Only 146 (20.1%) of the 726 inpatients had treatment that was in alignment with the Toward Optimized Practice IDA guideline.

Conclusions: There was substantial variation in baseline hemoglobin, mean corpuscular volume, and ferritin, and in the use of oral iron before initiation of IV iron treatment. Provision of educational tools and stewardship initiatives may help in ensuring alignment of iron prescribing with current guidelines.

Keywords: iron deficiency anemia, parenteral iron, iron sucrose, stewardship

RÉSUMÉ

Contexte : L'administration de fer par intraveineuse (IV) convient au traitement de l'anémie ferriprive lorsque son administration par voie orale n'a pas été efficace, tolérée ou appropriée d'un point de vue clinique. À Calgary (Alberta), il a fallu réviser les quantités de fer administrées par IV en raison de la mobilisation importante des ressources de soins de santé et des coûts élevés que cela exigeait ainsi que de l'accessibilité réduite au produit.

Objectifs : L'objectif principal consistait à décrire la population de patients adultes, dont le taux estimé de filtration glomérulaire était supérieur ou égal à 30 mL/min/1,73 m^2 et à qui on administrait du fer par IV dans des installations de soins intensifs de Calgary. La description devait se faire en termes de données de laboratoire préalables au traitement, d'administration antérieure de fer par voie orale et de lieu du traitement; il s'agissait aussi de décrire la dose et la sélection du produit pour l'administration de fer par IV. L'objectif secondaire consistait à déterminer la proportion de patients hospitalisés, dont le traitement s'alignait sur les directives de pratique clinique *Toward Optimized Practice* relatives à l'anémie ferriprive.

Méthodes : Un examen rétrospectif des tableaux électroniques a permis d'obtenir des données sur les patients, ayant reçu une première dose de fer par IV dans les hôpitaux de Calgary, entre le 1er mars et le 31 décembre 2018. Les données ont fait l'objet d'une analyse descriptive.

Résultats : Au total, 1352 patients répondaient au critère d'inclusion. Ils ont reçu 3532 doses de fer par IV, dont 97,1 % de saccharose de fer à raison d'une médiane de 300 mg par perfusion. Les indices de laboratoire évalués avant la première perfusion concernaient l'hémoglobine (moyenne 92, écart-type [ET] 19,6 g/L), le volume corpusculaire moyen (moyenne 81 [ET 10,3] fL) et la ferritine (moyenne 18 [écart interquartile 9-48] µg/L). Parmi les patients de l'étude, 233 (17,2 %) avaient reçu du fer par voie orale 90 jours avant la première dose de fer administrée par IV. Seuls 146 (20,1 %) des 726 patients hospitalisés avaient reçu un traitement conforme aux directives de pratique clinique *Toward Optimized Practice* relatives à l'anémie ferriprive.

Conclusions : On a constaté une variation importante de l'hémoglobine de base, du volume corpusculaire moyen et de la ferritine, ainsi que de l'utilisation du fer par voie orale avant le début du traitement par IV. Des outils pédagogiques et des initiatives de gestion pourraient aider à assurer l'alignement de la prescription de fer sur les directives actuelles.

Mots-clés : anémie ferriprive, fer administré par voie parentérale, fer-saccharose, gérance

INTRODUCTION

Iron deficiency anemia (IDA) is estimated to affect 1% to 2% of adults, accounting for approximately 50% to 80% of anemia cases worldwide.[1-3] Common presentations include symptoms of anemia, such as fatigue, skin pallor, and shortness of breath, as well as signs that are more specific to iron deficiency, including pica, restless legs, and hair loss or damage.[2] Complications associated with IDA include impaired quality of life, decreased work productivity, depression, and reduced cognitive functioning.[2,4] The diagnosis is based on hemoglobin (Hb), mean corpuscular volume (MCV), and ferritin values below designated levels, which vary slightly among guidelines.[1,2,5,6] Ferritin is the most accurate marker for detecting iron deficiency; however, other iron studies can be considered when the results of ferritin testing are indeterminate.[5]

Pharmacologically, the mainstays of treatment for iron deficiency are the orally administered iron salts: ferrous sulfate, gluconate, and fumarate.[1,2,4,7] Oral ferrous salts are widely available, inexpensive, and safe; however, they are associated with a high rate of gastrointestinal adverse effects, often resulting in nonadherence.[4,5] Newer formulations of oral iron, including iron polysaccharide complex and heme iron polypeptide, may be better tolerated but are more expensive and no more effective in correcting anemia than other iron salts.[6,8]

IV administration of iron is indicated when blood loss exceeds the absorptive capacity for iron, which may occur with uterine bleeding, hemodialysis, or iron malabsorption syndromes or when oral iron is not tolerated or is ineffective.[1,2,7,9] It can also be considered when Hb concentration is less than 60 g/L and rapid correction of iron stores is needed, or in circumstances when transfusion is contraindicated.[6,7,10] IV iron administration has the advantages of fewer gastrointestinal side effects, improved adherence, and more rapid iron replacement and correction of anemia.[4,11] However, data are insufficient to suggest a benefit over oral iron in terms of important clinical outcomes, such as mortality, blood transfusion requirements, and length of hospital stay.[12-15] Other potential concerns with IV iron include infusion reactions, the discomfort and inconvenience of IV administration, increased drug cost, and higher utilization of health care resources.[4,6]

In Alberta, IV iron products are becoming more frequently prescribed, with expenditures increasing 78% between 2015 and 2019 and representing 4.6% of the provincial acute care drug budget in the 2018/19 fiscal year (unpublished data). IV iron administration accounts for approximately 20% of visits to Calgary Zone Day Medicine departments and has been trending upward in recent years.[16] Initiatives to reduce the use of blood transfusions may have been a factor contributing to this increase.[16] Interest in optimizing anemia management prompted Alberta Health Services (AHS) to host the Iron Summit Conference in 2017, which aimed to identify gaps and opportunities and propose solutions to the management of IDA in the Calgary Zone.[16] During the summit it was suggested that some referrals for IV iron may not have been appropriate.[16] Furthermore, in cases of drug shortages from manufacturers, many medical specialists reported inconsistencies in their ability to access IV iron because of limited availability of outpatient appointments.[16] In March 2018, the Toward Optimized Practice (TOP) clinical practice guideline for IDA was published to provide prescribing guidance for primary care and emergency department practitioners in Alberta and thus support consistent management of IDA.[6,16] The TOP, now known as the Accelerating Change Transformation Team or ACTT, is a program supported by the Alberta Medical Association that enhances practice through provision of clinical practice guidelines, among other initiatives, primarily directed toward primary care physicians. Calgary clinicians have shown support for the concept of incorporating the TOP IDA treatment algorithm into eligibility criteria for access to parenteral iron.[6,16]

It is currently unknown whether certain patient-specific factors contribute to potential gaps in optimal prescribing of IV iron in Calgary. The overall objective of this study was to describe the characteristics of adult patients receiving IV iron to better understand prescribing patterns and identify target areas where initiatives to optimize iron usage could be focused. The TOP IDA clinical practice guideline was used as the basis for comparison to identify these target areas. More specifically, the primary objective was to describe adult patients with estimated glomerular filtration rate (eGFR) greater than or equal to 30 mL/min/1.73 m^2 for whom IV iron was dispensed, in terms of their pretreatment laboratory data, previous use of oral iron, and treatment location, as well as to characterize dose and product selection for IV iron. The secondary objective was to determine the proportion of inpatients whose treatment was in alignment with the TOP IDA clinical practice guideline.

METHODS

Study Design

A retrospective chart review was conducted in adult patients for whom IV iron was dispensed at any of the 4 adult tertiary care hospitals in Calgary in 2018. These facilities provide inpatient and ambulatory health care services to more than 1.6 million people from Calgary and the surrounding area.[17]

Study Population

Patients who were 18 years of age or older, had an eGFR greater than or equal to 30 mL/min/1.73 m^2, and had their first dose of IV iron dispensed between March 1 and December 31, 2018, were included in the study. Participants were drawn from both inpatient and ambulatory care settings. To determine which patients received their first dose of IV iron

on or after March 1, 2018, all IV iron doses dispensed to the target population between January 1 and December 31, 2018, were reviewed, and patients who received doses between January 1 and February 28, 2018, were excluded.

Chronic kidney disease is known to contribute to iron deficiency and is a well-recognized indication for IV iron; however, the TOP IDA guideline excludes patients with chronic kidney disease from its recommendations, and there are local practice documents for this patient group.[6] As such, patients with eGFR less than 30 mL/min/1.73 m^2 at the most recent measurement before administration of the first IV iron dose were excluded. All creatinine results reported through Alberta Health Services Analytics include the eGFR, which is calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[18]

Data Sources

Patients were identified using BDM Pharmacy (BDM Healthware Inc), the dispensing software used in Calgary hospitals, which contains patients' demographic information and details about IV iron doses dispensed, including dose (mg), formulation (iron sucrose, sodium ferric gluconate, or iron dextran), date dispensed, and treatment location. The laboratory values pertinent to the inclusion and exclusion criteria and study outcomes (eGFR, Hb, MCV, and ferritin) were obtained through Alberta Health Services Analytics. Dispensing data for oral iron products, including ferrous sulfate, ferrous gluconate, ferrous fumarate, polysaccharide iron complex, and heme iron polypeptide, were obtained from the Pharmaceutical Information Network, the electronic database in Alberta that captures outpatient prescriptions and dispensed schedule II products, including the aforementioned oral iron products. Sunrise Clinical Manager (Allscripts Healthcare, LLC), the electronic medical records program used in Calgary hospitals, was used to review discharge summaries for collection of symptom data for the inpatient population.

Outcomes

Adult patients with eGFR of 30 mL/min/1.73 m^2 or above who received IV iron were described in terms of pretreatment laboratory indices, including Hb, MCV, and ferritin. The proportion of patients with a previous trial of oral iron and a description of IV iron prescriptions, including formulation, doses of IV iron, and treatment setting in which they were received, were also evaluated. A previous trial of oral iron was defined as any oral iron dispensed (as documented in the Pharmaceutical Information Network) within 90 days before initiation of IV iron, as this represents a reasonable duration for trialling oral iron therapy and a typical maximum dispensing interval in Alberta. Additionally, the proportion of inpatients whose treatment was in alignment with the TOP IDA guideline treatment algorithm, based on pretreatment laboratory indices and the presence or absence of anemia symptoms, was determined. It was not feasible to report this outcome for the outpatient cohort, because the information required to determine the presence or absence of symptoms was not readily available through the selected methodology. The TOP guideline was chosen because it is current, was created locally, and has been supported by Alberta physicians and other health care providers.[16] Furthermore, provincial AHS guidelines were not yet in place at the time of this study. For IV iron use to be warranted, according to this guideline, a patient must meet laboratory criteria for diagnosis (Table 1) and must have either Hb less than 60 g/L or Hb less than 100 g/L in combination with symptoms of anemia.[6] For patients in the inpatient cohort who met the laboratory criteria for IDA diagnosis but had Hb between 60 and 100 g/L, discharge summaries were reviewed for the presence of symptomatic anemia, which was defined as documentation in the chart of IDA symptoms as set out in the TOP guideline treatment algorithm or synonyms of these terms or acceptable abbreviations (Table 2).

Patient Characteristics and Data Collection

Demographic data were collected for each patient, including age and sex. IV iron doses were assessed for administration location (inpatient or ambulatory), and specific treatment units were noted. Data for IV iron doses were reviewed from January 1, 2018, until the end of the study time frame to ensure that the sample included only patients who received their first dose after the release of the TOP IDA guideline in March 2018. Laboratory indices, including eGFR, Hb, MCV, and ferritin, and records of oral iron dispensed, obtained from the Pharmaceutical Information Network, were collected for all patients who met the inclusion criteria.

Statistical Analysis

Descriptive statistics were used to describe the study population and IV iron doses. Continuous variables were described using means and standard deviations (SDs) for normally distributed variables or medians and interquartile ranges (IQRs) for variables without a normal distribution. Categorical variables were expressed using frequency counts and proportions. All statistics, as well as the creation of tables and graphs, were completed using Excel 2013 (Microsoft Corporation).

TABLE 1. Laboratory Criteria for Diagnosis of Iron Deficiency Anemia, Based on the Toward Optimized Practice Clinical Practice Guideline[6]

	Sex; Criterion Value	
Criterion	**Male**	**Female**
Hemoglobin (g/L)	< 135	< 120
	Plus at least one of the following:	
Mean corpuscular volume (fL)	< 75	< 75
Ferritin (µg/L)	< 30	< 13

TABLE 2. Symptoms of Anemia, Accepted Synonyms, and Abbreviations

Symptom[a]	Acceptable Synonyms and Abbreviations
Shortness of breath	Dyspnea SOB
Chest pain	Chest discomfort CP
Light-headedness	Fainting or feeling faint Dizziness
Syncope	Presyncope Fainting Altered, impaired, or reduced level of consciousness
Suspected ongoing bleeding	Hematochezia Melena Hematuria Hematemesis Hematoma Gastrointestinal bleed (GI bleed, GIB) Bleeding Bleed Estimated blood loss (EBL)

[a]As per treatment algorithm of Toward Optimized Practice Iron Deficiency Anemia Committee.[6]

Ethics Approval

Ethics approval was obtained from the Health Research Ethics Board – Health Panel of the University of Alberta, with a waiver of consent granted.

RESULTS

A total of 1616 patients had dispensing of their first dose of IV iron between March 1 and December 31, 2018, and had prior measurement of eGFR. Of these patients, 261 (16.2%) were excluded because eGFR was less than 30 mL/min/1.73 m^2. Three additional patients were excluded after it was determined that none of their prescribed doses had been administered. A total of 1352 patients met the inclusion criteria and were included in the outcome analyses (Figure 1).

Baseline characteristics, including age, sex, treatment setting, and details of IV iron doses, are presented in Table 3. In total, 233 (17.2%) patients had received oral iron within 90 days before their first IV iron dose, as indicated by listing of an oral iron product in the Pharmaceutical Information Network. Half of all IV iron doses captured were dispensed to Day Medicine departments, the majority of which were iron sucrose (Table 3).

The overall mean Hb concentration measured before the first IV iron infusion within the study period was 92 (SD 19.6) g/L. Of all patients, 412 (30.5%) had pretreatment Hb above 100 g/L, the most frequently reported range (Figure 2). Twelve (2.6%) of the 463 men and 112 (12.6%) of the 889 women had Hb within normal limits, as defined in the TOP guideline[6] (Table 1).

The mean MCV for these patients was 81 (SD 10.3) fL, and 368 (27.2%) of the patients had MCV less than 75 fL, consistent with the TOP guideline criteria for diagnosis of IDA[6] (Table 1). Among the included patients, 1207 (89.3%) had ferritin measurement before their first dose of IV iron (Figure 3), with the median value being 18 (IQR 9–48) µg/L. Among those with pretreatment measurement of ferritin, 588 (48.7%) met the TOP criteria for diagnosis of IDA.

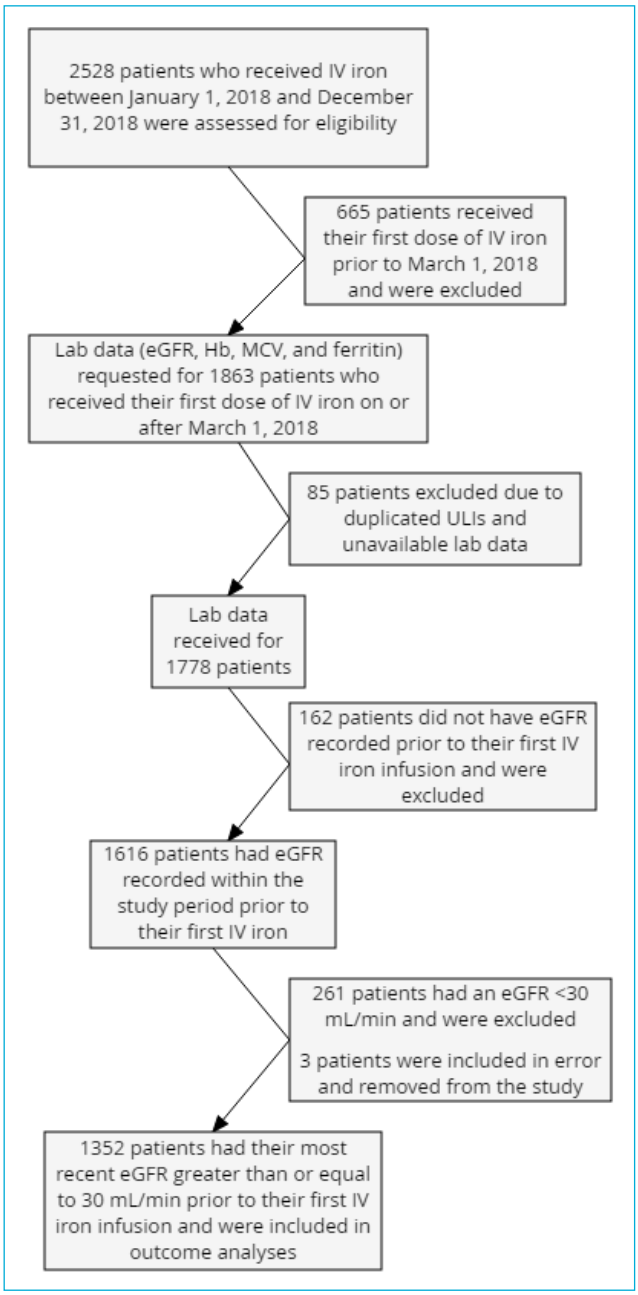

FIGURE 1. Study inclusion flow chart. eGFR = estimated glomerular filtration rate, Hb = hemoglobin, MCV = mean corpuscular volume, ULI = unique lifetime identifier (standard identification number assigned to all patients receiving health care in Alberta).

TABLE 3. Baseline Characteristics and IV Iron Data

Characteristic	No. (%)[a]	
Age (years) (median and IQR)	58	(41–74)
Sex	*n* = 1352 patients	
Male	463	(34.2)
Female	889	(65.8)
Patients by treatment setting	*n* = 1352 patients	
Inpatient	726	(53.7)
Outpatient	626	(46.3)
Doses by treatment setting	*n* = 3532 doses	
Inpatient	1573	(44.5)
Outpatient	1959	(55.5)
Doses by IV iron formulation	*n* = 3532 doses	
Iron sucrose	3430	(97.1)
Sodium ferric gluconate complex	102	(2.9)
IV iron dose description		
Mean dose per dose dispensed	262.5 mg	
Median dose per dose dispensed	300 mg	
Mean total dose dispensed per patient	685.6 mg	
Mean no. of IV iron doses per patient	2.6 doses	

IQR = interquartile range.
[a] Except where indicated otherwise.

Overall, the TOP laboratory criteria for IDA diagnosis, based on Hb, MCV, and ferritin (Table 1),[6] were fulfilled by 648 (47.9%) of the included patients. Of the 726 patients in the inpatient cohort, 146 (20.1%) had either Hb below 100 g/L and documented symptoms of anemia or Hb below 60 g/L, thus warranting the use of IV iron according to the TOP guideline. The proportions of patients meeting the diagnostic criteria and receiving IV iron according to guideline parameters were similar for men and women. For 7 inpatients, no discharge summary was available, and it could not be confirmed whether their treatment was in alignment with TOP recommendations.

DISCUSSION

In Calgary, the increasing utilization of IV iron has raised drug expenditures and reduced clinic capacity. This increase in IV iron utilization may be explained in part by recent initiatives to support appropriate use of red blood cell transfusions. For example, recent Choosing Wisely recommendations include avoiding transfusions in hemodynamically stable patients with IDA, with consideration of iron replacement instead.[16] When appropriate, IV iron products are a safe and less expensive alternative to blood transfusions; however, the acquisition cost for IV iron products and the resources required for their preparation, administration, and monitoring are significantly greater than those required for oral iron. Furthermore, given the limited availability of appointments in Day Medicine departments and frequent

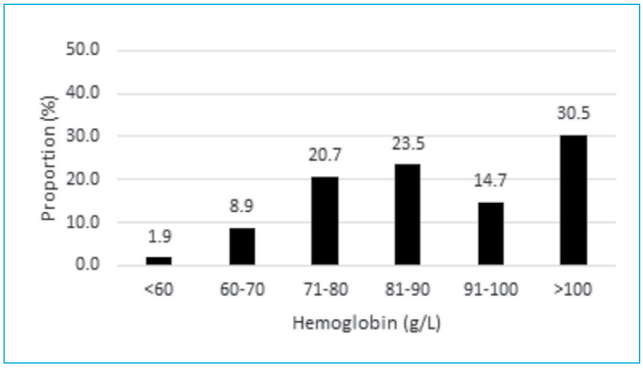

FIGURE 2. Distribution of hemoglobin values among patients who had measurement of hemoglobin before the first iron infusion (within the study time frame) (*n* = 1351).

drug shortages, overprescribing can hinder access for those who more urgently require IV iron or space in Day Medicine for other treatments.

The TOP guideline proposes Hb, MCV, and ferritin as the criteria for laboratory diagnosis and monitoring of IDA, consistent with recommendations elsewhere in the literature.[1,4-7,9] In this study, approximately half of the patients for whom IV iron was prescribed met the laboratory criteria for diagnosis of IDA. These results suggest that these laboratory indices and/or the criteria in the TOP guideline are not being consistently applied in the diagnosis and treatment of IDA in Calgary and that there may be significant room for optimizing the use of IV iron. Although the method used did not take into account other indications for IV iron, such as malabsorption syndromes and blood loss exceeding the absorptive capacity of iron, it is unlikely that these conditions would make up for the large discrepancy between the guideline and clinical use. When each laboratory parameter was evaluated individually, the majority of patients had Hb meeting the suggested criteria, whereas fewer than half met the criteria for MCV and ferritin (Table 1). Furthermore, only 1207 of the 1352 patients had ferritin levels measured

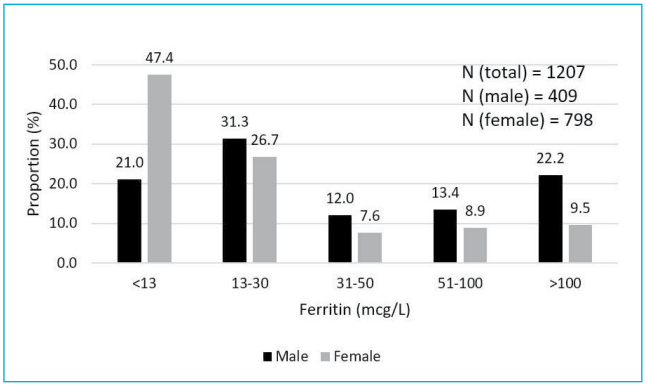

FIGURE 3. Distribution of ferritin values among patients who had measurement of ferritin before the first iron infusion (within the study time frame) (*n* = 1207).

before their first IV iron infusion, which highlights the potential for a more comprehensive use of ferritin before IV iron is initiated.

The existing literature describing appropriate IV iron utilization is sparse and often limited to studies with small sample sizes. A 2007 audit of iron utilization in the Ulster Hospital, Northern Ireland, evaluated 47 patients who received IV iron and determined that 45% were not treated according to local guidelines.[19] A small prospective study in the AHS South Zone in 2017 evaluated 17 patients who received IV iron; 6 (35%) of these patients were not treated according to prespecified criteria (Barnson C, Fong V. A snapshot of intravenous iron infusions at Chinook Regional Hospital [CRH] and eight surrounding rural sites over a five day time period; unpublished report). Of the 726 inpatients in the current study, only 146 (20.1%) were treated in alignment with the TOP guideline. This result was limited by the retrospective study design, which allowed evaluation of laboratory data and discharge summaries only; however, given the low rates described with these limited data, it is possible that prescribing is infrequently concordant with guidelines.

Another factor that may be considered when prescribing IV iron is whether there has been an adequate trial of oral iron in the past. In the current study, Pharmaceutical Information Network profiles for the majority of patients showed no record of oral iron within 90 days before the first IV iron dose. It is difficult to interpret this result, because these profiles capture information only for schedule II oral iron products provided in the community pharmacy setting, with no information about adherence, duration of use, or provision of oral iron in the inpatient setting. This study suggests that IV administration of iron is being prescribed regardless of whether an oral iron product has been trialled previously; further study is required to confirm this finding.

Although pregnancy status was not captured, the proportion of women of child-bearing age within the study sample was substantially greater than the proportion of men in the same age group (Figure 4). This is likely because of higher iron requirements and the prevalence of IDA in menstruating and pregnant women.[6,9] Iron supplementation is often recommended for pregnant women, because maternal IDA may increase the risk of preterm delivery, low birth weight,[6,10] and, in severe cases, increased maternal and neonatal mortality.[10] However, pregnancy alone does not always necessitate the preferential use of IV iron over oral formulations. A 2019 systematic review and meta-analysis comparing IV and oral administration of iron to pregnant women showed that IV administration was associated with statistically significant but modest increases in maternal Hb and ferritin at delivery and in birth weight; however, the clinical relevance of these results remains in question, and data on other important clinical outcomes are limited.[20]

This study was limited by the use of retrospective data from electronic sources, which precluded a more accurate evaluation of each patient's history, symptoms, specific IV iron indication, and comorbidities. Additionally, IV iron dispensed to Day Medicine departments at 2 of the included hospitals could not be analyzed because parenteral iron is prepared using ward stock at these sites; therefore, doses could not be attributed to specific patients using the BDM Pharmacy software. As a result, ambulatory patients were underrepresented in this study relative to inpatients. Furthermore, the use of blood products was not evaluated. Patients in this study might have received transfusions before the first IV iron infusion, which may have modified laboratory markers for anemia and affected the categorization of study results. Thus, evaluating the appropriateness of IDA management, including transfusion medicine and the use of iron products, remains an important topic for future research. With regard to previous use of oral iron, limiting the fill dates for oral iron to 90 days before a patient's first IV iron dose might have resulted in underestimation of patients who had previously trialled oral iron if this form of therapy was tried and failed before this time frame. Additionally, there is a possibility that not all of the oral iron dispensed was captured by the Pharmaceutical Information Network. Finally, the TOP IDA guideline is intended for use in emergency departments and primary care settings; as such, using this guideline to

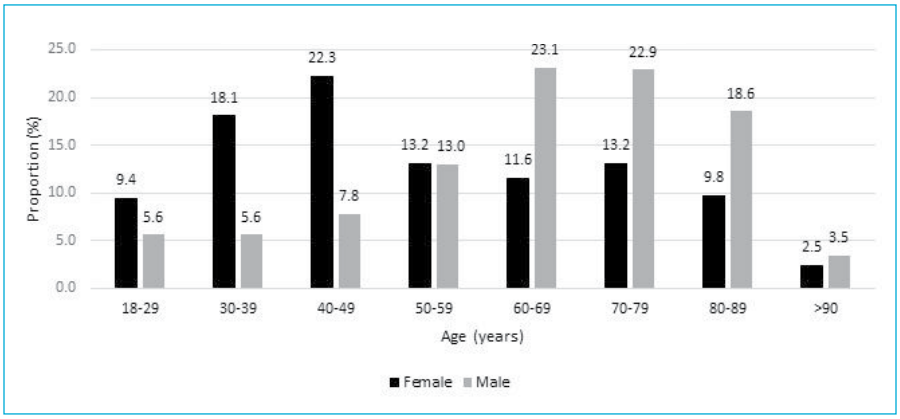

FIGURE 4. Age distribution of included patients (n = 1352).

evaluate the appropriateness of IV iron prescribing for inpatients is not optimal.[6] However, a local guideline more suitable for this population was not available.

CONCLUSION

The results presented here suggest that the use of IV iron in the study jurisdiction was often not aligned with guidelines, including laboratory and clinical criteria for this type of therapy. A potential strategy to promote consistency of diagnosis and treatment would be for the province to adopt a single guideline, such as the TOP guideline, with concomitant provision of practice tools incorporating TOP recommendations to optimize iron prescribing. The creation of a central iron clinic, with multidisciplinary teams to evaluate parenteral iron referrals for appropriateness before administration of the first dose, has also been proposed.[16] Formulary restriction of IV iron products to patients meeting prespecified criteria, based on relevant laboratory tests, comorbidities, and previous use of oral iron may also be considered. Implementing such strategies will require collaboration among multidisciplinary stakeholders across the province to ensure that implemented measures improve the cost-effective use of iron products and access to outpatient Day Medicine programs, without creating barriers to parenteral iron products for those who require them. Further research is needed to fully characterize the treatment of IDA in other jurisdictions and across various specialties to ensure effective stewardship of the resources used to manage this common condition.

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Stability of Generic Formulations of Bortezomib 1.0 and 2.5 mg/mL in Vials and Syringes Stored at 4°C and Room Temperature (23°C or 25°C)

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ABSTRACT

Background: The availability of generic versions of bortezomib raises questions about the reliability of extrapolating stability data from one brand to another.

Objective: To evaluate the stability of bortezomib formulations available from Janssen, Teva Canada, Actavis Pharma, Dr. Reddy's Laboratories, Apotex, and MDA, reconstituted with 0.9% sodium chloride (normal saline) to produce solutions of either 1.0 or 2.5 mg/mL and stored over at least 21 days under refrigeration (4°C) or at room temperature (either 23°C or 25°C) in the manufacturer's original glass vials or in polypropylene syringes.

Methods: On study day 0, solutions with concentration 1.0 mg/mL or 2.5 mg/mL of the Teva, Actavis, Dr. Reddy's, Apotex, and MDA generic formulations were prepared. Three units of each type of container (glass vials and syringes) were stored at 4°C and 3 units at room temperature. Concentration and physical inspection were completed on at least 8 study days (including day 0) over a 21- to 84-day study period. Bortezomib concentrations were determined by a validated stability-indicating liquid chromatographic method with ultraviolet detection. The end point of these studies was the time to reach 90% of the initial concentration (T-90) with 95% confidence, which is expressed as "$T\text{-}90_{95\%CI}$", where CI refers to the confidence interval. In addition to estimating the $T\text{-}90_{95\%CI}$, differences in stability among products from all manufacturers were compared using multiple linear regression. Previously published data for the Janssen product were included in the overall comparisons.

Results: In all of the studies, the analytical method separated degradation products from bortezomib, such that the concentration of bortezomib was measured specifically, accurately (deviations < 2.5%), and reproducibly (average replicate error 2.5%). During all studies, solutions retained more than 94% of the initial concentration at 4°C. The $T\text{-}90_{95\%CI}$ exceeded the study period for all formulations under all combinations of concentration, container, and temperature, except the 84-day study for the MDA product. Multiple linear regression showed no significant differences among manufacturers ($p = 0.57$).

Conclusions: In this study, formulations of bortezomib currently marketed in Canada (by Janssen, Teva Canada, Actavis Pharma, Dr. Reddy's Laboratories, Apotex, and MDA) were pharmaceutically equivalent and interchangeable. Given that there was no difference in stability related to manufacturer, nominal concentration, or container, we conclude that these formulations are physically and chemically stable for at least 35 days under refrigeration and at least 25 days at room temperature.

Keywords: bortezomib, stability, generic formulation stability, beyond-use date

RÉSUMÉ

Contexte : La disponibilité de versions génériques de bortezomib soulève des questions relatives à la fiabilité de l'extrapolation des données concernant la stabilité d'une marque à l'autre.

Objectif : Évaluer la stabilité des formules de bortezomib de Janssen, de Teva Canada, d'Actavis Pharma, des Laboratoires du Dr Reddy, d'Apotex et de MDA, reconstituées avec 0,9 % de chlorure de sodium (solution saline normale) pour produire des solutions de 1 ou de 2,5 mg/mL et réfrigérées au moins 21 jours à 4 °C ou à température ambiante (23 °C ou 25 °C), dans des fioles en verre du fabricant ou dans des seringues en polypropylène.

Méthodes : La préparation des solutions avec une concentration de 1 mg/mL ou 2,5 mg/mL des formules génériques de Teva, d'Actavis, du Dr Reddy, d'Apotex et de MDA a eu lieu le jour 0 de l'étude. Trois unités de chaque contenant (fioles en verre et seringues) étaient stockées à 4 °C et 3 unités, à température ambiante. L'inspection de la concentration et l'inspection physique ont été réalisées pendant au moins 8 jours (y compris le jour 0) de l'étude qui a duré de 21 à 84 jours. Les concentrations de bortezomib ont été déterminées par une méthode chromatographique liquide validée, indiquant la stabilité à l'aide d'une détection par rayons ultraviolets. Le point final de ces études était le temps nécessaire pour que le produit atteigne 90 % de la concentration initiale (T-90) avec un seuil de confiance de 95 %, exprimé par $T\text{-}90_{IC\ 95\ \%}$, IC indiquant l'intervalle de confiance. En plus de l'estimation du $T\text{-}90_{IC\ 95\ \%}$, les différences de stabilité des produits de tous les fabricants ont été comparées à l'aide d'une régression linéaire multiple. Les données publiées précédemment sur le produit Jansen sont incluses dans les comparaisons globales.

Résultats : La méthode analytique de toutes les études qui ont été menées a séparé les produits de dégradation du bortezomib de telle manière que la concentration était mesurée de manière spécifique, précise (déviations < 2,5 %) et reproductible (erreur de réplique 2,5 %). Tout au long des études, les solutions ont retenu plus de 94 % de la concentration initiale à 4 °C. Le $T\text{-}90_{IC\ 95\ \%}$ de toutes les formules dans toutes les combinaisons de concentration, de contenant et de température, dépassait la durée des études, à l'exception du produit MDA dans l'étude de 84 jours. La régression linéaire multiple n'a indiqué aucune différence importante parmi les fabricants ($p = 0,57$).

Conclusions : Dans cette étude, les formules de bortezomib actuellement commercialisées au Canada (par Janssen, Teva Canada, Actavis Pharma, les Laboratoires du Dr Reddy, Apotex et MDA) étaient équivalentes et interchangeables d'un point de vue pharmaceutique. Puisqu'aucune différence de stabilité, de concentration nominale ou de contenant liée à l'un ou l'autre des fabricants n'a été révélée, nous concluons que ces formules sont physiquement et chimiquement stables pendant au moins 35 jours sous réfrigération et au moins 25 jours à température ambiante.

Mots-clés : bortezomib, stabilité, stabilité de formule générique, date limite d'utilisation

INTRODUCTION

Bortezomib is indicated for the treatment of patients with previously untreated multiple myeloma for whom stem cell transplant is unsuitable, for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy, and for the treatment of patients with mantle cell lymphoma who have experienced relapse or whose disease was refractory to at least 1 prior therapy.[1-6] It is available in Canada from multiple manufacturers as 3.5 mg of sterile lyophilized powder in a 10-mL clear glass vial for reconstitution with 0.9% sodium chloride (normal saline [NS]).[1-6]

Product monographs from 6 manufacturers of this drug—Janssen, Teva Canada, Actavis Pharma, Dr. Reddy's Laboratories, Apotex, and MDA—state that the total storage time of a reconstituted solution with concentration 1 mg/mL or 2.5 mg/mL, in the manufacturer's original vial or after transfer to a syringe, must not exceed 8 h at room temperature with exposure to normal indoor lighting.[1-6] A study published in this Journal in 2008 demonstrated that 1 mg/mL solutions of bortezomib prepared from the Janssen formulation (Velcade), intended for IV administration, retained more than 95% of the initial concentration for up to 42 days when stored at either 4°C or 23°C.[7] A study reported in *Lancet Oncology* in 2011 demonstrated that in 222 patients, there was no significant difference in time to progression or 1-year overall survival with subcutaneous (SC) or IV bortezomib, although adverse events were significantly fewer with SC administration. SC injections are administered as 2.5 mg/mL (3.5 mg bortezomib reconstituted with 1.4 mL of NS) to limit the volume injected.[8] Given that SC administration achieved equal efficacy with a reduction in adverse events, the SC route has become the preferred method of administration. A study published in 2014 demonstrated that a 2.5 mg/mL solution of bortezomib in the original manufacturer's vial (Velcade, Janssen), intended for SC administration, retained more than 94% of the initial concentration for up to 21 days when stored at either 4°C or 23°C.[9]

In 2015, Teva launched a generic version of bortezomib, followed by the release of other generics by Actavis in late 2015 and Dr. Reddy's in early 2017.[10] Other formulations received a Notice of Compliance in Canada in 2019, including those manufactured by Apotex, Marcan, MDA, PharmaScience, Pfizer, and Sandoz.[10] Many of the manufacturers have requested stability studies of their respective formulations to provide evidence for use beyond the expiry time identified in the respective product monographs (i.e., 8 h at 23°C).[1-6]

The objective of the research reported here was to evaluate the stability of 5 generic bortezomib products. Each study was conducted separately in the same laboratory, near the time of launch for each formulation. Each formulation was reconstituted in accordance with the manufacturer's recommendations with either 1.4 mL of NS to produce a 2.5 mg/mL solution or 3.5 mL of NS to produce a 1.0 mg/mL solution. The reconstituted solutions were stored in the original manufacturer's glass vial or polypropylene syringes, and the stability was evaluated after storage under refrigeration (4°C) or at room temperature (either 23°C or 25°C).

Some pharmacists have interpreted the guidelines of the National Association of Pharmacy Regulatory Authorities (NAPRA)[11] as requiring that each institution conduct separate evaluations of the stability of the formulation or manufacturer's product used in that institution. Therefore, a secondary objective was to compare the results of these studies to determine if there were any differences in stability among manufacturers' formulations and, if the products were found to be similar, to recommend that the products be considered pharmaceutically equivalent and interchangeable. Such a finding may be important, especially in the event of a drug shortage. Two different brands of polypropylene syringes were used in the course of the study. Differences in stability attributable to differences in the storage container were evaluated as part of the assessment of drug formulations from different manufacturers.

METHODS

Materials

Each of the 6 available formulations of bortezomib for injection contains 3.5 mg of bortezomib as a mannitol boronic ester. The only nonmedicinal ingredient is mannitol. The products do not contain any preservatives, buffers, or antioxidants.[1-6]

Chromatographic Analysis

The stability-indicating method of André and others[12] was modified and revalidated in our laboratory before the initial 2008 study.[7] All subsequent investigations were conducted using the same analytical method, according to accepted criteria.[13-15] The liquid chromatographic system consisted of a solvent delivery pump (model P4000, Thermo Fisher Scientific Separation Products), which pumped a mixture of 30% acetonitrile and 70% 0.05 M potassium phosphate dibasic (high-performance liquid chromatography [HPLC] grade, catalogue no. P3786, Sigma Aldrich). The pH of the buffer was adjusted to 6.8 with concentrated phosphoric acid (HPLC grade, catalogue no. A260-500, Fisher Scientific) before mixing with acetonitrile. On each analysis day, the mobile phase was prepared to achieve a retention time for bortezomib of about 6.6 min through a 15 cm × 4.6 mm reversed-phase C-18 5-µm column (Supelco ABZ+, Waters Scientific) at 1.0 mL/min. A 2-µL quantity of each prepared sample, quality control solution, and standard was injected directly onto the liquid chromatographic column using an autoinjector (Ultra WISP 715, Waters Scientific), in duplicate.

The column effluent was monitored with a variable-wavelength ultraviolet detector (UV6000, Thermo Fisher Scientific) at 270 nm. The signal from the detector was integrated and recorded with a chromatography data system

(ChromQuest, version 5.0, Thermo Fisher Scientific). The area under the bortezomib peak at 270 nm was subjected to least-squares linear regression, and the actual bortezomib concentration in each sample was determined by interpolation from the standard curve.

Assay Validation

Following the set-up of the chromatographic system for bortezomib as described in the 2008 article,[7] the suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of bortezomib with various concentrations of sodium hypochlorite. The contents of a 3.5-mg vial of bortezomib (bortezomib mannitol boronic ester for injection, Velcade, Janssen Ortho Inc; lot 4CBS301, expiry March 2006) was dissolved in 3.5 mL of distilled water to prepare a 1 mg/mL solution.[7] The mixture was vortex-mixed and chromatographed immediately. Chromatograms from all samples were inspected for the appearance of additional peaks, and the bortezomib peak was compared between samples for changes in concentration, retention time, and peak shape (electronic overlay and numeric calculation of tailing). UV spectral purity (200–365 nm, 6-nm bandwidth, deuterium lamp; determined with UV6000 system, Thermo Fisher Scientific) of the bortezomib peak in a chromatogram of a degraded sample produced by sodium hypochlorite was compared with the spectrum of the authentic, undegraded sample of bortezomib in water obtained at time 0.

To revalidate the specificity of the system before each study, a 2.5 mg/mL solution of bortezomib was intentionally degraded using 5 µL of 0.3% sodium hypochlorite (sodium hypochlorite 0.5%, PCS 5000 oxidizing disinfectant, Process Cleaning Solutions, Peterborough, Ontario; lot 096133, expiry September 30, 2019; diluted with distilled water).

After this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.[16]

Stability Study

Similar to the method used in the prior studies of the Janssen formulation,[7,9] on study day 0 of each of the generic bortezomib studies, each of twelve 3.5-mg vials of bortezomib mannitol boronic ester for injection (Teva, lot 1590615, expiry June 2018; Actavis, lot EF16005C, expiry June 2018; Dr. Reddy's, lot H7005, expiry December 2019; Apotex, lot BORAC1048, expiry November 2020; MDA, lot 1802580G, expiry July 2021) was reconstituted with 3.5 mL of NS to prepare 1.0 mg/mL solutions. The contents of 6 vials of each company's formulation were drawn into 3-mL polypropylene Becton-Dickinson syringes (Teva, Actavis, and Dr. Reddy's formulations) or 3-mL polypropylene Equashield closed system transfer syringes (Apotex and MDA formulations); the remaining 6 reconstituted solutions were left in the manufacturers' glass vials. In each study, 3 of the 6 vials and 3 of the 6 syringes were stored at room temperature (23°C ± 2°C or 25°C ± 2°C), protected from fluorescent room light; the other 3 syringes and 3 vials were stored in the refrigerator (4°C) without exposure to fluorescent lighting.

Similarly, on study day 0 of each of the generic bortezomib studies, each of twelve 3.5-mg vials was reconstituted with 1.4 mL of NS to prepare 2.5 mg/mL solutions. The contents of 6 vials of each company's formulation were drawn into 3-mL polypropylene Becton-Dickinson syringes (Teva, Actavis, and Dr. Reddy's formulations) or 3-mL polypropylene Equashield closed system transfer syringes (Apotex and MDA formulations); the remaining 6 reconstituted solutions were left in the manufacturers' glass vials. In each study, 3 of the 6 vials and 3 of the 6 syringes were stored at room temperature (23°C ± 2°C or 25°C ± 2°C), protected from fluorescent room light; the other 3 syringes and 3 vials were stored in the refrigerator (4°C) without exposure to fluorescent lighting.

Study Days

Sampling days were slightly different during each study, according to when the study was completed and the manufacturer's desire to replicate the original study design, as reported in 2008.[7] For the Actavis and Dr. Reddy's formulations, 8 sampling days occurred over a 21-day study period (days 0, 1, 2, 5, 7, 11, 14, and 21). For the Teva formulation, 10 sampling days occurred over a 42-day study period (0, 1, 3, 7, 10, 14, 22, 28, 34, and 42). For the Apotex formulation, 11 sampling days occurred over a 42-day period (0, 1, 4, 8, 11, 15, 18, 21, 28, 35, and 42). For the MDA formulation, 11 sampling days occurred over 84 days (0, 1, 2, 3, 7, 10, 14, 21, 35, 62, and 84).

Bortezomib Analysis

On each study day, a 3.5-mg vial of bortezomib from each manufacturer (Teva, lot 1590615, expiry June 2018; Actavis, lot EF16005C, expiry June 2018; Dr. Reddy's, lot H7005, expiry December 2019; Apotex, lot BORAC1048, expiry November 2020; MDA, lot 1802580G, expiry July 2021) was reconstituted with 1.167 mL of distilled water to make a 3 mg/mL solution. On each study day, this stock solution was further diluted to prepare standards with final concentrations of 3.000, 2.250, 1.125, 0.563, and 0.375 mg/mL. When combined with a blank, these standards served to construct a standard curve. In addition, 2 quality control samples with bortezomib concentrations of 0.75 and 1.5 mg/mL were prepared from this same stock solution. A 2-µL quantity of each standard, sample, or quality control solution was chromatographed in duplicate without further dilution. Intraday and interday errors were assessed by the coefficients of variation (CVs) of the peak areas of both the quality control samples and the standards.

On each study day for each manufacturer, samples drawn from each of the 3 vials and 3 syringes stored at each of the 2 temperatures were assayed for bortezomib content. All samples initially contained a nominal concentration of

1.0 mg/mL or 2.5 mg/mL of bortezomib. A 2-µL quantity of each sample was injected directly onto the liquid chromatographic system without further preparation, in duplicate, to ensure the ability to distinguish concentrations in vials with concentrations that differed by 10% or more.[17,18]

Physical Stability

On each study day, samples drawn for concentration analysis were inspected visually for changes in colour and particulate matter against a white and a black background.

Data Reduction and Statistical Analysis

After determining the CV of the assay, a power calculation showed that duplicate injection had the ability to distinguish between concentrations that differed by at least 10% within each type of container.[17,19] Means were calculated for replicate analyses. Mean results from different days for each test were compared statistically to determine whether an association existed between the observed result and time. The percent remaining was analyzed by linear regression, and a 95% confidence interval (CI) was constructed around the slope of percent remaining versus study days. The time to reach 90% of the initial concentration (T-90) with 95% confidence (expressed as "$T\text{-}90_{95\%CI}$") was calculated from the time (in days) for the lower limit of the 95% CI to reach 90%. Analysis of variance was used to test differences in concentration on different study days, with different initial nominal concentrations, different containers, and different storage temperatures. The 5% level was used as the a priori cut-off for significance.

Bortezomib concentrations were considered "acceptable" or "within acceptable limits" if the lower limit of the 95% confidence limit of concentration remaining was greater than 90% ($T\text{-}90_{95\%CI}$) of the initial (day 0) concentration.

Manufacturer Comparison

Identifying potential differences in stability between manufacturers was also an objective of this study. Bortezomib stability data for the Janssen formulation (the innovator product) for the 1.0 mg/mL concentration (published in 2008)[7] and the 2.5 mg/mL concentration (published in 2014)[9] were included in the evaluation. The primary end point of all of the individual studies was the time to reach 90% of the initial concentration, with 95% confidence ($T\text{-}90_{95\%CI}$). This end point involves the construction of a confidence interval; therefore, although the value of $T\text{-}90_{95\%CI}$ is based on the change in percent remaining (degradation rate, expressed as percentage per day), it is also a function of variability in the data (standard deviation of regression) and number of study days (ranging between 8 and 11). To ensure homogeneity of the data across all 6 formulations, the standard deviation of regression observed for each combination of initial nominal concentration, container type, storage temperature, and manufacturer was compared using analysis of variance and linear regression.

In the evaluation of manufacturer, a variable for manufacturer was added to the same multiple linear regression model (IBM SPSS Statistics, version 20.0.0) used in individual studies with a constant (effectively time 0 of 100%). In this analysis, study data for percent remaining from all formulations on each study day were pooled and analyzed using the variables study day, initial nominal concentration, storage temperature, type of container, and manufacturer. Other potential factors, such as number of study days and study duration, were not included in this analysis because of their correlation with manufacturer. The 5% level was used as the a priori cut-off for significance.

RESULTS

Accelerated Degradation and Assay Validation

As reported previously,[7,9] degradation of bortezomib with sodium hypochlorite occurs quickly. At 23°C, addition of 5 µL of a 0.5% solution of sodium hypochlorite to a 1.0 mg/mL solution of bortezomib in water led to immediate degradation, with 6.32% of the original concentration remaining. Solutions containing lower concentrations of sodium hypochlorite degrade bortezomib more slowly. When 5 µL of a 0.25% solution of sodium hypochlorite was added to bortezomib (2.5 mg/mL), 42.38% of the original concentration remained when the sample was chromatographed immediately. The treated solutions contained degradation products of bortezomib, which eluted at 2.0 and 5.5 min (Figure 1). Additional peaks were observed to elute at 14.5 min and between 2 and 4.5 min when solutions of sodium hypochlorite with concentration above 0.4% were added. None of these degradation products interfered with quantification of bortezomib, and the UV spectrum of the bortezomib peak (200–365 nm) in a degraded sample was no different than the spectrum of the authentic, undegraded standard. The retention times reported in this study are slightly different from retention times reported in previous articles[7,9]; however, all validation studies showed separation of the degradation products from bortezomib, and none of the degradation products in any study interfered with quantification of bortezomib. When compared with the chromatograms published by André and others,[12] the chromatograms are virtually identical to those produced with hydrogen peroxide. Hydrogen peroxide and sodium hypochlorite generate all of the degradation products produced by acid, base, and/or heat, as well as 2 additional degradation products, which eluted in our system at 6.5 and 14.5 min.

As a result of the chromatographic separation of these degradation products from bortezomib, and the similarity of the UV spectrum (200–365 nm) between an authentic standard and bortezomib in a degraded sample, it was concluded that this was a stability-indicating analytical method.[13-15]

Analysis of standard curves and quality control samples during each study showed an average absolute deviation from

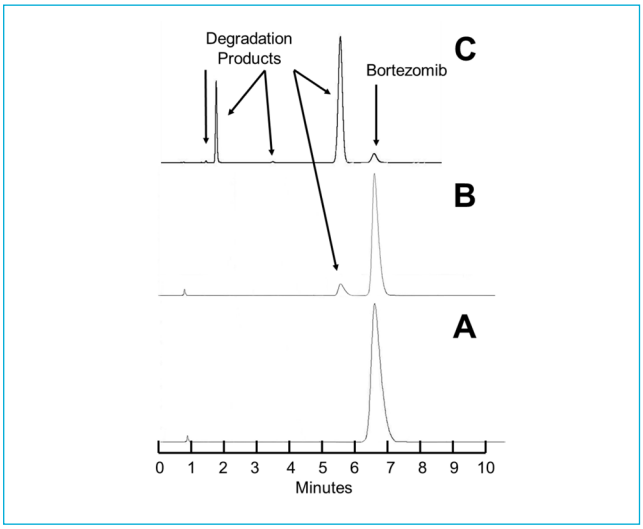

FIGURE 1. Chromatograms of bortezomib 2.5 mg/mL in water under various degradation conditions. (A) Before addition of sodium hypochlorite. (B) Immediately after addition of 5 µL of 0.25% sodium hypochlorite; 42.38% of the original compound remains. (C) Immediately after addition of 5 µL of 0.5% sodium hypochlorite; 6.32% of the original compound remains. Visually evident degradation products appeared at 2.0 and 5.5 min.

the expected concentration of 2.50% for the Teva product, 2.18% for the Actavis product, 1.91% for the Dr. Reddy's product, 2.17% for the Apotex product, and 2.10% for the MDA product. The standard deviation of regression was 1.02% for the Teva product, 0.82% for the Actavis product, 0.76% for the Dr. Reddy's product, 1.06% for the Apotex product, and 1.02% for the MDA product. Analytical reproducibility, within a day (as measured by the CV), averaged 1.02% for the Teva product, 0.90% for the Actavis product, 0.62% for the Dr. Reddy's product, 0.44% for the Apotex product, and 0.36% for the MDA product.

These results indicate that analytical performance was similar for each of the separate studies and that differences in concentration of 10% or more could be confidently detected within individual containers with acceptable error rates.[17,18]

Bortezomib Stability Studies

In all studies, all solutions stored in either the original manufacturer's glass vials or the polypropylene syringes were initially clear and colourless and remained unchanged for the duration of the study period. No visible particles were observed in any solution in any of the studies.

Concentrations observed during each study of the bortezomib solutions with nominal concentrations of 1.0 mg/mL and 2.5 mg/mL are presented in Table 1 (Teva), Table 2 (Actavis), Table 3 (Dr. Reddy's), Table 4 (Apotex), and Table 5 (MDA). Bortezomib concentrations were considered "acceptable" or "within acceptable limits" if the lower limit of the 95% confidence interval of concentration remaining was greater than 90% of the initial (day 0) concentration ($T\text{-}90_{95\%CI}$). Using this criterion, the shortest time to reach the lowest acceptable concentration for the 5 generic products, with storage at 4°C, was calculated to be 60.27 days for the Teva formulation (Table 1), 35.42 days for the Actavis formulation (Table 2), 37.21 days for the Dr. Reddy's formulation (Table 3), 64.85 days for the Apotex formulation (Table 4), and 95.71 days for the MDA formulation (Table 5). For each formulation, the shortest time exceeded the study duration for that formulation and averaged about 30% longer than the time to reach the lowest acceptable concentration for the 5 generic products with storage at 23°C or 25°C. At room temperature, the $T\text{-}90_{95\%CI}$ was 46.45 days for the Teva formulation (Table 1), 25.72 days for the Actavis formulation (Table 2), 31.41 days for the Dr. Reddy's formulation (Table 3), 56.70 days for the Apotex formulation (Table 4), and 57.67 days for the MDA formulation (Table 5). For all but one of the formulations, the shortest time exceeded the study duration for that formulation; the exception was the MDA formulation, which had the longest study duration (84 days). In that study, after 84 days of storage at room temperature, approximately 87%–89% of the initial concentration remained, and a degradation product, observed during the accelerated study with elution at 5.5 min, was observed in chromatograms (Figure 2).

Analysis of variance detected differences in the percent remaining of 1% or less. In every study, significant changes in concentration due to study day ($p < 0.001$) and temperature ($p < 0.001$) were detected. Only the Actavis study demonstrated a difference related to either container or concentration, and in both cases the difference was less than 1%.

Manufacturer Comparisons

Data from the 5 studies of generic formulations and the previously published studies of the Janssen product[7,9] are summarized in Table 6. All of these studies, including the original studies of the Janssen formulation, were completed in the same laboratory over an 11-year period, using the same analytical method. The primary end point of each study was an evaluation of the degradation rate and the shortest time to reach 90% of the initial concentration with 95% confidence ($T\text{-}90_{95\%CI}$). Because confidence intervals are involved in calculation of the $T\text{-}90_{95\%CI}$, this end point is dependent on variability in the data. To ensure homogeneity within the data set, the standard deviations of regression observed for each combination of concentration, container type, storage temperature, and manufacturer were compared. The standard deviation of regression varied from 0.354% to 1.967%. Analysis of variance detected no significant differences in the standard deviation of regression due to the factors of manufacturer ($p = 0.81$), storage temperature ($p > 0.99$), concentration ($p = 0.64$), type of container ($p = 0.17$), or study duration ($p = 0.31$). Furthermore, there was no correlation between the standard deviation of regression and the time to reach 90% of the initial concentration with 95% confidence

TABLE 1. Measured Concentrations[a] of Bortezomib from Teva and Percent Remaining on Each Study Day

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		23°C[b]		4°C		23°C[b]	
Variable	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]
Observed initial concentration (mg/mL)[a] ± CV	1.12±3.20	1.09±3.10	1.10±1.03	1.11±1.53	2.42±3.32	2.33±1.42	2.47±1.52	2.33±0.06
Study day								
1	100.21±2.26	100.36±1.51	99.95±1.60	97.89±1.67	100.35±0.57	100.87±0.47	99.63±0.17	102.56±0.26
3	99.82±2.86	100.54±1.42	100.91±2.80	98.45±1.20	100.51±1.10	100.32±1.28	100.18±0.76	99.59±0.82
7	99.50±2.61	101.11±3.17	100.95±2.47	98.80±0.90	100.94±1.23	100.27±0.83	100.26±0.61	99.89±0.19
10	100.29±2.81	102.30±2.92	102.98±2.83	99.38±1.20	101.17±2.82	100.42±1.02	99.63±0.52	99.41±0.83
14	102.89±1.74	101.87±3.52	100.99±2.25	99.23±0.78	100.39±3.27	99.39±0.65	99.49±1.46	99.91±0.20
22	99.21±2.47	99.86±3.16	96.63±1.17	96.08±1.41	96.75±3.20	97.81±0.81	98.21±5.44	98.36±1.31
28	97.58±1.23	98.46±2.24	98.77±2.26	98.64±0.88	97.19±2.73	99.26±2.17	98.20±1.95	98.50±0.93
34	97.22±1.83	99.69±3.73	96.96±1.82	97.13±0.80	96.62±0.97	99.43±1.96	97.50±0.95	95.53±1.32
42	96.52±1.55	98.15±1.87	94.95±2.44	95.97±2.11	97.15±1.03	98.77±1.66	96.73±1.40	95.62±1.98
Degradation rate (%/day) (slope)[d]	−0.091	−0.058	−0.133	−0.065	−0.110	−0.044	−0.081	−0.128
Correlation coefficient (*r*)	−0.727	−0.646	−0.798	−0.695	−0.851	−0.703	−0.963	−0.894
Standard deviation of regression (*Sy*.x)[e]	1.340	1.074	1.573	1.048	1.063	0.688	0.354	0.999
Confidence interval for slope[f]	±0.06994	±0.05605	±0.08213	±0.05473	±0.05549	±0.03593	±0.01850	±0.05213
Fastest degradation rate (%/day) with 95% confidence	−0.1609	−0.1142	−0.2153	−0.1195	−0.1659	−0.0795	−0.0991	−0.1800
Slowest degradation rate (%/day) with 95% confidence	−0.0210	−0.0021	−0.0510	−0.0101	−0.0549	−0.0077	−0.0621	−0.0757
Shortest T-$90_{95\%CI}$ in days[g]	62.15	87.60	46.45	83.65	60.27	125.74	100.88	55.56

CI = confidence interval, CV = coefficient of variation.

[a]Concentrations are expressed as the percent remaining ± standard deviation (except where indicated otherwise). Percent remaining was calculated from the concentration, determined in duplicate, of each of 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

[b]Room temperature was 23°C ± 2°C.

[c]Becton-Dickinson syringe with a polypropylene barrel.

[d]The degradation rate (slope) was determined by linear regression of the percent remaining on each study day.

[e]The standard deviation of regression, *Sy*.x, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

[f]The confidence interval for the degradation rate allows calculation of the fastest and slowest degradation rates with 95% confidence (degradation rate ± confidence interval).

[g]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-$90_{95\%CI}$ uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

TABLE 2. Measured Concentrations[a] of Bortezomib from Actavis and Percent Remaining on Each Study Day

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		23°C[b]		4°C		23°C[b]	
Variable	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]
Observed initial concentration[a] (mg/mL) ± CV	1.05±1.84	1.04±2.04	1.01±0.14	1.04±2.68	2.45±0.70	2.44±0.81	2.46±0.37	2.46±0.14
Study day								
1	99.93±0.70	99.11±1.72	99.89±2.11	99.09±0.81	101.15±1.65	101.61±0.49	100.84±0.31	100.72±0.28
2	98.37±0.20	98.83±0.47	99.14±1.69	98.59±1.51	100.74±1.02	100.25±0.70	100.00±0.37	98.77±0.82
5	98.25±0.88	98.81±1.14	97.66±0.46	98.72±1.13	99.54±1.72	99.74±1.13	97.99±0.64	99.20±0.44
7	99.31±1.70	98.51±1.27	96.70±0.93	96.34±1.95	100.14±1.81	99.79±1.48	98.88±0.60	96.93±1.43
11	98.09±0.26	99.24±1.82	96.84±0.30	96.33±1.61	98.77±3.23	96.94±0.50	96.48±1.07	95.79±0.68
14	98.70±2.17	98.34±0.76	96.66±0.43	96.14±1.31	98.91±2.47	97.70±1.02	96.72±0.57	95.48±0.65
21	98.59±1.46	98.29±0.95	95.81±0.34	95.64±0.88	100.73±1.45	99.36±1.48	96.14±0.62	95.79±0.71
Degradation rate (%/day) (slope)[d]	–0.051	–0.053	–0.200	–0.203	–0.032	–0.120	–0.226	–0.250
Correlation coefficient (*r*)	–0.495	–0.679	–0.897	–0.891	–0.270	–0.596	–0.907	–0.875
Standard deviation of regression (*Sy.x*)[e]	0.704	0.447	0.774	0.815	0.908	1.277	0.828	1.090
Confidence interval for slope[f]	±0.08936	±0.05677	±0.09817	±0.10338	±0.11516	±0.16199	±0.10505	±0.13824
Fastest degradation rate (%/day) with 95% confidence	–0.1403	–0.1094	–0.2977	–0.3068	–0.1475	–0.2824	–0.3310	–0.3887
Slowest degradation rate (%/day) with 95% confidence	0.0384	0.0042	–0.1014	–0.1001	0.0828	0.0416	–0.1210	–0.1122
Shortest T-$90_{95\%CI}$ in days[g]	71.26	91.43	33.59	32.59	67.79	35.42	30.21	25.72

CI = confidence interval, CV = coefficient of variation.

[a]Concentrations are expressed as the percent remaining ± standard deviation (except where indicated otherwise). Percent remaining was calculated from the concentration, determined in duplicate, of each of 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

[b]Room temperature was 23°C ± 2°C.

[c]Becton-Dickinson syringe with a polypropylene barrel.

[d]The degradation rate (slope) was determined by linear regression of the percent remaining on each study day.

[e]The standard deviation of regression, *Sy.x*, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

[f]The confidence interval for the degradation rate allows calculation of the fastest and slowest degradation rates with 95% confidence (degradation rate ± confidence interval).

[g]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-$90_{95\%CI}$ uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

TABLE 3. Measured Concentrations[a] of Bortezomib from Dr. Reddy's and Percent Remaining on Each Study Day

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		23°C[b]		4°C		23°C[b]	
Variable	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]
Observed initial concentration (mg/mL)[a] ± CV	1.01±2.09	0.98±0.55	0.99±1.15	0.98±0.13	2.50±0.41	2.50±0.40	2.51±0.43	2.49±0.57
Study day								
1	100.01±1.31	98.75±0.78	100.40±1.57	100.46±1.28	100.56±2.15	99.68±0.39	98.86±0.15	99.07±0.40
2	100.03±0.99	99.88±0.21	100.02±2.33	100.65±0.66	99.61±0.90	100.22±0.04	99.59±0.70	99.20±0.32
5	97.95±0.78	99.21±0.75	97.96±0.19	98.07±0.43	99.49±2.53	99.94±0.12	98.08±0.43	97.09±1.38
7	97.88±0.41	99.14±0.77	96.88±1.34	97.43±1.18	99.49±2.50	99.73±0.84	97.62±0.45	97.14±1.11
11	96.36±0.74	97.66±0.23	98.45±0.87	99.07±0.44	99.57±2.67	98.54±0.61	97.83±0.73	96.10±1.13
14	97.90±0.54	99.64±0.79	96.80±1.50	97.23±0.40	98.07±2.85	97.31±0.22	96.36±0.91	95.57±0.38
21	97.50±0.83	99.88±1.07	95.92±0.10	96.79±0.34	98.13±0.13	97.70±0.32	96.42±0.91	96.67±1.18
Degradation rate (%/day) (slope)[d]	−0.142	−0.001	−0.203	−0.172	−0.104	−0.139	−0.167	−0.177
Correlation coefficient (*r*)	−0.743	−0.007	−0.870	−0.813	−0.881	−0.894	−0.907	−0.800
Standard deviation of regression (*Sy*.x)[e]	1.003	0.847	0.906	0.966	0.440	0.549	0.610	1.045
Confidence interval for slope[f]	±0.12726	±0.10748	±0.11493	±0.12256	±0.05581	±0.06968	±0.07734	±0.13261
Fastest degradation rate (%/day) with 95% confidence	−0.2688	−0.1082	−0.3183	−0.2941	−0.1598	−0.2087	−0.2442	−0.3096
Slowest degradation rate (%/day) with 95% confidence	−0.0143	0.1067	−0.0885	−0.0490	−0.0481	−0.0693	−0.0895	−0.0444
Shortest T-$90_{95\%CI}$ in days[g]	37.21	92.41	31.41	34.00	62.59	47.92	40.96	32.30

CI = confidence interval, CV = coefficient of variation.

[a]Concentrations are expressed as the percent remaining ± standard deviation (except where indicated otherwise). Percent remaining was calculated from the concentration, determined in duplicate, of each of the 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

[b]Room temperature was 23°C ± 2°C.

[c]Becton-Dickinson syringe with a polypropylene barrel.

[d]The degradation rate (slope) was determined by linear regression of the percent remaining on each study day.

[e]The standard deviation of regression, *Sy*.x, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

[f]The confidence interval for the degradation rate allows calculation of the fastest and slowest degradation rates with 95% confidence (degradation rate ± confidence interval).

[g]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-$90_{95\%CI}$ uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

TABLE 4. Measured Concentrations[a] of Bortezomib from Apotex and Percent Remaining on Each Study Day

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		25°C[b]		4°C		25°C[b]	
Variable	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]	Vial	Syringe[c]
Observed initial concentration (mg/mL)[a] ± CV	1.04±0.16	1.05±0.59	1.05±0.53	1.05±0.36	2.46±0.35	2.48±0.13	2.45±0.16	2.47±0.31
Study day								
1	99.61±0.76	98.64±0.80	98.54±0.23	98.88±0.30	100.40±0.57	99.82±0.69	100.61±0.65	100.20±0.16
4	99.64±0.23	98.73±0.67	99.38±0.32	99.14±0.56	100.14±1.04	99.49±1.03	100.45±0.34	99.15±0.48
8	101.63±0.40	100.84±0.63	99.94±0.72	100.35±0.77	103.42±0.69	103.29±0.36	99.88±0.37	100.01±1.04
11	99.51±0.32	99.37±0.57	99.76±0.33	99.21±0.78	103.55±1.11	102.38±0.02	99.80±1.33	98.01±0.30
15	99.51±0.06	98.18±1.44	98.21±0.25	98.19±0.53	97.54±0.56	97.17±0.44	97.23±1.83	97.20±0.67
18	99.53±0.38	100.78±0.21	98.27±0.48	98.74±0.32	102.86±1.10	102.25±0.11	98.59±0.66	97.55±0.69
21	101.12±0.18	100.27±0.91	98.72±2.57	97.16±0.26	101.44±0.60	100.67±0.35	97.25±0.14	97.36±0.47
28	98.05±0.22	97.75±0.67	97.87±0.98	96.19±0.80	99.18±0.28	98.57±0.46	96.64±0.16	96.27±0.36
35	99.28±0.06	98.53±0.60	96.31±0.54	96.01±0.46	99.12±0.15	98.52±0.69	95.21±0.34	96.41±3.61
42	99.75±0.05	98.15±0.28	95.23±0.51	95.04±0.40	98.72±0.35	98.20±0.14	94.95±0.12	95.10±0.31
Degradation rate (%/day) (slope)[d]	−0.019	−0.032	−0.096	−0.117	−0.053	−0.058	−0.144	−0.117
Correlation coefficient (*r*)	−0.287	−0.397	−0.890	−0.928	−0.364	−0.412	−0.958	−0.944
Standard deviation of regression (*Sy.x*)[e]	0.944	1.069	0.723	0.684	1.967	1.867	0.628	0.594
Confidence interval for slope[f]	±0.0487	±0.0552	±0.0373	±0.0353	±0.1015	±0.0964	±0.0324	±0.0307
Fastest degradation rate (%/day) with 95% confidence	−0.0681	−0.0868	−0.1337	−0.1518	−0.1542	−0.1541	−0.1764	−0.1472
Slowest degradation rate (%/day) with 95% confidence	0.0293	0.0236	−0.0591	−0.0812	0.0488	0.0386	−0.1116	−0.0859
Shortest T-$90_{95\%CI}$ in days[g]	146.75	115.26	74.77	65.85	64.85	64.87	56.70	67.93

CI = confidence interval, CV = coefficient of variation.

[a]Concentrations are expressed as the percent remaining ± standard deviation (except where indicated otherwise). Percent remaining was calculated from the concentration, determined in duplicate, of each of 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

[b]Room temperature was 25°C ± 2°C.

[c]Equashield closed system transfer syringe with a polypropylene barrel.

[d]The degradation rate (slope) was determined by linear regression of the percent remaining on each study day.

[e]The standard deviation of regression, *Sy.x*, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

[f]The confidence interval for the degradation rate allows calculation of the fastest and slowest degradation rates with 95% confidence (degradation rate ± confidence interval).

[g]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-$90_{95\%CI}$ uses the fastest degradation rate, determined from the 95% confidence limit of the slope.

TABLE 5. Measured Concentrations[a] of Bortezomib from MDA[b] and Percent Remaining on Each Study Day

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		25°C[c]		4°C		25°C[c]	
Variable	Vial	Syringe[d]	Vial	Syringe[d]	Vial	Syringe[d]	Vial	Syringe[d]
Observed initial concentration (mg/mL)[a] ± CV	1.04±0.09	1.05±0.59	1.04±0.22	1.05±0.10	2.45±0.37	2.45±0.44	2.45±0.48	2.45±0.43
Study day								
1	100.22±0.51	99.98±0.20	99.47±0.38	99.29±0.12	100.41±0.84	100.64±0.32	99.13±0.37	99.50±0.27
2	98.95±0.39	98.62±1.06	98.92±0.54	98.68±0.72	99.50±1.31	99.55±0.28	98.81±0.29	99.50±0.79
3	99.36±0.69	100.57±0.59	98.99±0.30	98.66±0.22	102.10±0.31	101.98±0.35	99.22±0.27	99.08±0.45
7	100.46±0.20	99.52±0.53	100.50±0.58	99.73±2.25	102.09±1.17	101.19±2.37	100.44±1.72	101.85±0.25
10	100.71±0.43	100.09±1.25	97.15±0.27	97.76±0.61	98.36±0.35	99.29±0.46	97.12±0.38	97.50±0.99
14	97.95±0.41	97.05±0.99	96.54±2.06	96.99±0.29	98.86±0.96	98.75±0.29	97.06±0.67	97.54±0.76
21	99.09±0.50	98.50±0.09	96.85±0.59	96.89±1.09	98.47±0.47	98.47±0.45	96.20±1.32	97.18±0.28
35	97.71±0.33	96.59±0.63	95.46±0.35	94.93±0.86	97.64±0.36	97.87±0.47	95.93±0.54	95.63±0.46
62	96.86±0.29	96.81±1.02	93.11±0.25	93.30±0.49	96.16±0.40	96.26±0.38	93.90±0.51	93.65±1.02
84	94.72±0.12	94.04±0.79	87.79±0.92	88.54±1.86	94.25±0.27	93.66±0.53	87.48±0.66	86.93±0.04
Degradation rate (%/day) (slope)[e]	−0.0590	−0.0643	−0.1282	−0.1202	−0.0755	−0.0793	−0.1256	−0.1380
Correlation coefficient (*r*)	−0.909	−0.889	−0.963	−0.977	−0.892	−0.939	−0.949	−0.947
Standard deviation of regression (*Sy.x*)[f]	0.792	0.970	1.050	0.769	1.125	0.854	1.227	1.376
Confidence interval for slope[g]	±0.02037	±0.02495	±0.02700	±0.01978	±0.02894	±0.02198	±0.03156	±0.03539
Fastest degradation rate (%/day) with 95% confidence	−0.0794	−0.0893	−0.1552	−0.1399	−0.1045	−0.1013	−0.1571	−0.1734
Slowest degradation rate (%/day) with 95 confidence	−0.0386	−0.0394	−0.1012	−0.1004	−0.0466	−0.0574	−0.0940	−0.1026
Shortest T-$90_{95\%CI}$ in days[h]	125.98	111.99	64.42	71.46	95.71	98.69	63.64	57.67

CI = confidence interval, CV = coefficient of variation.

[a]Concentrations are expressed as the percent remaining ± standard deviation (except where indicated otherwise). Percent remaining was calculated from the concentration, determined in duplicate, of each of 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

[b]MDA Inc recently changed its name to Juno Pharmaceuticals Corp.

[c]Room temperature was 25°C ± 2°C.

[d]Equashield closed system transfer syringe with a polypropylene barrel.

[e]The degradation rate (slope) was determined by linear regression of the percent remaining on each study day.

[f]The standard deviation of regression, *Sy.x*, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

[g]The confidence interval for the degradation rate allows calculation of the fastest and slowest degradation rates with 95% confidence (degradation rate ± confidence interval).

[h]The T-90 is the time for the concentration to decline by 10%, i.e., to reach 90% of the initial concentration. The shortest T-$90_{95\%CI}$ uses the fastest degradation rate determined from the 95% confidence limit of the slope.

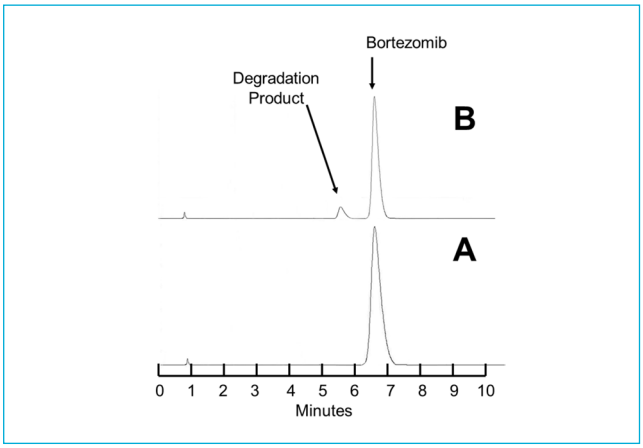

FIGURE 2. Chromatograms of bortezomib 2.5 mg/mL, reconstituted in normal saline and stored in syringes at room temperature (25°C) during the MDA stability study. (A) On study day 0. (B) After 84 days of storage at room temperature. Very small amounts of a degradation product originally observed during the accelerated degradation study were observed in solutions stored at room temperature.

($T\text{-}90_{95\%CI}$) ($r^2 = 0.0009$, $n = 46$, $p = 0.84$). These results indicate that the standard deviation of regression is effectively a random variable in the analysis.

In the pooled analysis of study data for percent remaining, using multiple linear regression, the results were similar to those seen in the individual formulation studies: only study day ($p < 0.001$) and temperature ($p < 0.001$) were identified as significant variables affecting the percent remaining. Manufacturer ($p = 0.57$) did not significantly affect the percent remaining. Nominal initial concentration ($p = 0.34$) and container ($p = 0.38$) were also not identified as significant factors. Given than the pooled analysis represented glass vials from 6 manufacturers and 2 different brands of polypropylene syringes (Becton-Dickinson and Equashield), this evaluation demonstrates that differences in container manufacturers also do not affect bortezomib stability.

Inspection of Table 6 shows that the shortest $T\text{-}90_{95\%CI}$ occurred in studies evaluating stability over 21 days, where the estimated value of $T\text{-}90_{95\%CI}$ averaged 47.1 days (range 25.7–92.4 days). In contrast, the average value of $T\text{-}90_{95\%CI}$ was 86 days for studies lasting 42 and 84 days (range 36.4–174.5 days). This should not be interpreted as indicating a difference in stability among the manufacturers. Because confidence intervals widen as they extend beyond the last study day, studies of shorter duration will generally intersect with a "90% remaining" limit earlier, even when the degradation rate (stability) is similar. Manufacturer was not identified as significantly affecting the percent remaining ($p = 0.57$) or the degradation rate ($p = 0.56$).

DISCUSSION

In each of the 5 studies of the stability of generic formulations of bortezomib, the solutions stored in manufacturers' vials and syringes, at the 2 concentrations tested (1 mg/mL and 2.5 mg/mL) and under 2 storage temperatures (4°C and room temperature), retained more than 90% of the initial concentration over the respective study period, except for solutions of the MDA formulation stored at room temperature. Similarly, the value of $T\text{-}90_{95\%CI}$ exceeded the study period for all formulations, except the MDA formulation stored at room temperature.

When the innovator stability data were pooled with data from the stability studies of the 5 generic formulations to evaluate the effect of manufacturer on the $T\text{-}90_{95\%CI}$, multiple linear regression detected no significant differences related to manufacturer ($p = 0.57$), type of container ($p = 0.38$), or initial nominal concentration ($p = 0.34$). As was the case in all of the individual studies, temperature ($p < 0.001$) and study day ($p < 0.001$) were significant factors in the pooled analysis. This brings into question the need for stability data specific to the manufacturer's formulation or container used in each institution. To obtain such data is a formidable and costly task. Most institutions are unable to conduct their own studies and must rely on published data or manufacturers' in-house data. When there are no published data demonstrating *differences* in stability between products from different manufacturers, it would appear to be unnecessary, financially burdensome, and contrary to the principle of evidence-based medicine to demand such data. In fact, we are aware of only 2 studies that compare stability of a particular product between manufacturers.[19,20] Both of these studies investigated the stability of vancomycin and reported no difference in stability due to the manufacturer, following dilution with NS or dextrose 5% in water.[19,20] Although some publications have reported that generic products are of inferior quality, these studies are frequently biased or poorly designed. Similarly, no differences due to manufacturer were observed in the current evaluation and previously published bortezomib studies.[7,9] Furthermore, every study generated a $T\text{-}90_{95\%CI}$ greater than 25 days, which is longer than any beyond-use date (BUD) permitted by the current (November 2016) NAPRA guidelines.[11]

Health Canada declares a new drug to be the "pharmaceutical equivalent" of another drug if it contains "identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients".[21] Even so, most manufacturers of generic IV formulations develop their respective formulations following analysis of the innovators' formulations, thereby achieving some degree of pharmaceutical equivalence. In this study, all 5 generic products had the same medicinal and nonmedicinal ingredients and were described virtually identically in the product monographs as follows: "bortezomib for injection is supplied in … vials containing 3.5 mg of bortezomib as a mannitol boronic ester, as a white to off-white cake or powder. The only nonmedicinal ingredient is mannitol."[1-6] The differences among the

TABLE 6. Summary of Bortezomib Stability Studies: Shortest Time to Reach 90% Remaining (with 95% Confidence)

	Nominal Concentration 1.0 mg/mL				Nominal Concentration 2.5 mg/mL			
	4°C		23°C or 25°C		4°C		23°C or 25°C	
Manufacturer and Variable	**Vial**	**Syringe**	**Vial**	**Syringe**	**Vial**	**Syringe**	**Vial**	**Syringe**
Janssen[a]								
Shortest T-90$_{95\%CI}$ in days[b]	93.84	Not tested	174.49	Not tested	51.48	50.07	37.26	36.36
Standard deviation of regression (*Sy.x*)[c]	1.099		0.941		0.660	0.873	0.745	0.763
Study duration (days)	42		42		21	21	21	21
Study days (no. of analysis days)	11		11		8	8	8	8
Teva								
Shortest T-90$_{95\%CI}$ in days[b]	62.15	87.60	46.45	83.65	60.27	125.74	100.88	55.56
Standard deviation of regression (*Sy.x*)[c]	1.340	1.074	1.573	1.048	1.063	0.688	0.354	0.999
Study duration (days)	42	42	42	42	42	42	42	42
Study days (no. of analysis days)	10	10	10	10	10	10	10	10
Actavis								
Shortest T-90$_{95\%CI}$ in days[b]	71.26	91.43	33.59	32.59	67.79	35.42	30.21	25.72
Standard deviation of regression (*Sy.x*)[c]	0.704	0.447	0.774	0.815	0.908	1.277	0.828	1.090
Study duration (days)	21	21	21	21	21	21	21	21
Study days (no. of analysis days)	8	8	8	8	8	8	8	8
Dr. Reddy's								
Shortest T-90$_{95\%CI}$ in days[b]	37.21	92.41	31.41	34.00	62.59	47.92	40.96	32.30
Standard deviation of regression (*Sy.x*)[c]	1.003	0.847	0.906	0.966	0.440	0.549	0.610	1.045
Study duration (days)	21	21	21	21	21	21	21	21
Study days (no. of analysis days)	8	8	8	8	8	8	8	8
Apotex								
Shortest T-90$_{95\%CI}$ in days[b]	146.75	115.26	74.77	65.85	64.85	64.87	56.70	67.93
Standard deviation of regression (*Sy.x*)[c]	0.944	1.069	0.723	0.684	1.967	1.867	0.628	0.594
Study duration (days)	42	42	42	42	42	42	42	42
Study days (no. of analysis days)	11	11	11	11	11	11	11	11
MDA (now known as Juno Pharmaceuticals Corp)								
Shortest T-90$_{95\%CI}$ in days[b]	125.98	111.99	64.42	71.46	95.71	98.69	63.64	57.67
Standard deviation of regression (*Sy.x*)[c]	0.792	0.970	1.050	0.769	1.125	0.854	1.227	1.376
Study duration (days)	84	84	84	84	84	84	84	84
Study days (no. of analysis days)	11	11	11	11	11	11	11	11

CI = confidence interval.

[a]Data published previously.[7,9]

[b]The T-90$_{95\%CI}$ is the time to reach 90% of initial concentration, with 95% confidence, based on the degradation rate and is generally regarded as the beyond-use date, where it does not exceed the duration of the study.

[c]The standard deviation of the regression, *Sy.x*, is equivalent to the interday variability (error) of the analytical method, expressed as a percentage.

products seem to be limited to the vial size (Teva is marketed in a 13.5-mL vial, whereas all others are supplied in 10-mL vials), with stoppers being specified as free of natural rubber latex for all except the Dr. Reddy's and Apotex products.

In many Canadian provinces, including Ontario, similarity in formulation that results in similar physical and chemical properties can form the grounds for a waiver of bioequivalence data.[22] When pharmaceutical equivalence results in similar physical and chemical properties (including pH and concentration), it is very likely to result in similar stability, as demonstrated by this study. Therefore, for drugs for which pharmaceutical equivalence has been demonstrated, with known chemical stability exceeding BUDs established by USP General Chapter <797>[23] and NAPRA,[11] extrapolating the BUD across manufacturers would seem reasonable, provided that within a particular institution, pharmacy practitioners can answer questions related to sterility and have knowledge of the institutional contamination rate.

CONCLUSION

We conclude that formulations of bortezomib currently marketed in Canada (manufactured by Janssen, Teva Canada, Actavis Pharma, Dr. Reddy's, Apotex, and MDA) are pharmaceutically equivalent and interchangeable. Based on the observation that there is no effect of manufacturer or nominal concentration on stability, using the shortest time to reach 90% of the initial concentration (with 95% confidence, T-$90_{95\%CI}$), we conclude that these formulations are physically and chemically stable for at least 35 days at 4°C and at least 25 days at room temperature.

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Implementation of Beyond-Use Date Guidelines for Single-Use Vials at a Pediatric Hospital

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INTRODUCTION

In September 2016, the National Association of Pharmacy Regulatory Authorities (NAPRA) published the *Model Standards for Pharmacy Compounding of Non-hazardous Sterile Preparations*[1] and the *Model Standards for Pharmacy Compounding of Hazardous Sterile Preparations*.[2] These documents introduced updated guidelines for establishing beyond-use dates (BUDs) for compounded sterile preparations. In addition to establishing BUDs for the preparations themselves, the guidelines stipulate the length of time that commercially available products used to compound a sterile preparation (either hazardous or nonhazardous) may be used following needle puncture. According to these updated guidelines, the BUD for commercially available single-use vials is 6 h after needle puncture, if kept in a primary engineering control with ISO Class 5 air quality. If, following needle puncture, the single-use vial is removed from the ISO Class 5 primary engineering control, it must be discarded. Furthermore, if a single-use vial is punctured or opened in an environment with air quality lower than ISO Class 5, the vial must be discarded after 1 h. The BUD for multiple-dose containers, which typically contain a preservative, is 28 days or the manufacturer's expiry date.

These updated BUD guidelines have important implications for compounding practices in hospital pharmacies because of the potential increase in medication wastage, which will occur if the 6-h BUD is reached before all of the vial contents are used. The Pharmacy Department at the Children's Hospital of Eastern Ontario (CHEO), in Ottawa, Ontario, conducted a study to evaluate medication wastage due to reaching the BUD for single-use vials as set out in the 2016 NAPRA model standards. The ultimate goal was to find a way to reduce waste and the costs associated with such waste. CHEO is a 167-bed pediatric hospital. Its Pharmacy Department is staffed by 19.6 full-time equivalent (FTE) pharmacy technicians and 16.7 FTE pharmacists. Each year, an average of 400 000 sterile preparations are compounded by the hospital's pharmacy staff.

The study was designed to determine actual wastage for a 1-week period under different conditions and then to extrapolate from these data to predict wastage over longer periods (1 month and 1 year). The overall study consisted of 3 wastage studies, each lasting 1 week, as described below. The 1-week duration was set in part because of operational and time constraints, but was also intended to capture typical workflows during the week and on the weekend, to reduce potential bias. Results from the 3 wastage studies were then compared with mathematically predicted wastage month-over-month on the basis of vials discarded from August 2018 to July 2019.

The protocol for the study described in this article was reviewed and approved by the Research Ethics Board of the CHEO Research Institute.

EVALUATION OF WASTAGE: ACTUAL AND EXTRAPOLATED VOLUMES OF WASTE

Wastage Study 1: Volume of Waste before Implementation of NAPRA 2016 BUD Guidelines

The first step of the evaluation was to document the cost of wastage produced in the Class 5 clean room of the CHEO pharmacy before implementation of the 2016 BUD guidelines.[1,2] The pharmacy's practice before implementation of the new guidelines was to discard single-use vials when either the volume remaining was insufficient to prepare a complete dose or the vial had expired (according to the manufacturer's guidelines). To determine overall wastage in terms of volume and cost, we collected from the clean room, over a 1-week period, every single-use vial and all compounded medication discarded for any reason. Over this 1-week period, the volume of medication remaining in each discarded single-use vial was completely extracted and measured using syringes (Table 1: volume wasted per week, before implementation of 6-h BUD). The cost of each discarded medication in single-use vials was obtained from pharmacy records. The cost of discarded compounded medications (per millilitre of reconstituted solution) was calculated using the

TABLE 1. Wastage Studies to Evaluate Mean Volume Wasted and Associated Costs

Wastage Study	Period; Volume Wasted (mL)[a]			Period; Cost of Wastage ($CAD)[b]		
	Per Week (Actual)	Per Month (Extrapolated)	Per Year (Extrapolated)	Per Week (Actual)	Per Month (Extrapolated)	Per Year (Extrapolated)
1: Before implementation of 6-h BUD	597	2602	31 226	399	1595	20 734
2: After implementation of 6-h BUD	1317	5740	68 875	1355	5420	70 456
3: After optimization of use of different-size vials with 6-h BUD	1110	4836	58 026	692	2768	35 987

BUD = beyond-use date.
[a] Volume of waste was rounded to the nearest millilitre.
[b] Cost of waste was rounded to the nearest dollar.

compounding prices available within the hospital's electronic medical record software. For each drug and concentration, the total volume wasted or lost during the week was calculated and multiplied by the determined price per millilitre. For the list of drugs used in Wastage Study 1, see Appendix 1 (available from https://cjhp.journals.publicknowledgeproject.org/index.php/cjhp/issue/view/202). The cost of wastage was then summed across all drugs to obtain the total cost of wastage during the week (Table 1: cost of wastage per week, before implementation of 6-h BUD).

Wastage Study 2: Volume of Waste after Implementation of NAPRA 2016 BUD Guidelines

The next step was to implement the new 6-h BUD guidelines. A label with the BUD (i.e., the date and time at which the vial was to be discarded) was added to each vial when it was punctured or reconstituted. After reconstitution in the primary engineering control, single-use vials were discarded after 6 h. Following implementation of the updated BUD guidelines, Wastage Study 2 was completed according to the methods described above for Wastage Study 1. Most of the vials collected during the 1-week period of Wastage Study 2 were antibiotics (for the list of drugs used in Wastage Study 2, see Appendix 2, available from https://cjhp.journals.publicknowledgeproject.org/index.php/cjhp/issue/view/202), which had to be reconstituted 3 times a day in order to comply with the new BUD guidelines.

Wastage Study 3: Volume of Waste after Vial-Size Optimization

Wastage Study 3 was undertaken to optimize the use of different vial sizes (as available from the manufacturer) to reduce waste and maximize the number of doses that could be reconstituted and administered before the BUD limits were reached. For each dose of each medication, the total amount of drug to be reconstituted was calculated to determine which size of vial would be most appropriate to use (for the list of drugs used in Wastage Study 3, see Appendix 3, available from https://cjhp.journals.publicknowledgeproject.org/index.php/cjhp/issue/view/202). For each drug, the different vial sizes available at the hospital were taken into account and the associated prices recorded. The number of smaller-size vials required to exceed the price of the larger-size vial was used to decide the total amount of medication to be compounded; this process created a threshold for determining the vial size that should be used when more than one size of vial existed for a given medication. The bigger vial size was used only if the total amount of the drug to be compounded was greater than the specified threshold. An optimal assortment of vials was then used.

For example, cefazolin is available at our hospital in 1-g and 10-g vials (see Table 2). According to prices obtained from our supplier, we determined that we could buy seven 1-g vials before reaching the cost of a 10-g vial. Therefore, to reduce waste and associated costs, when 6 g or less is to be compounded at the same time, the smaller (1-g) vials must be used. When more than 6 g is to be compounded at the same time, the larger (10-g) vial must be used. That is deducted from the total amount, and the other vials needed are evaluated with the same method. For example, in practice, for a total amount of 12 g, most of the doses will be prepared from a 10-g vial, with the remainder being prepared from two 1-g vials. The vial-size optimization table (Table 2) was explained to the technicians who actually perform sterile compounding at CHEO, and smaller vials were made available in the anteroom of the clean room, such that all vial sizes were easily accessible for the technicians. Following vial-size optimization, a third 1-week wastage study was conducted, the results of which are also presented in Table 1 (volume wasted and cost of wastage per week, after optimization of use of different-size vials).

Comparison of Wastage across Studies

Table 1 allows comparison of data from the 3 wastage studies, showing first that the mean volume of wastage over 1 week increased upon implementation of the 6-h BUDs,

TABLE 2. Optimization of Use of Different-Size Vials for Selected Drugs[a]

Drug	Vial Size[b]	Total Amount of Drug Suitable for Vial Size[c]
Acyclovir	500 mg 1000 mg	For doses ≤ 500 mg, use 500-mg vial For doses > 500 mg, use 1000-mg vial
Caspofungin	50 mg 70 mg	For doses ≤ 50 mg, use 50-mg vial For doses > 50 mg, use 70-mg vial
Cefazolin	1 g 10 g	For doses ≤ 6 g, use 1-g vials For doses > 6 g, use 10-g vial
Ceftazidime	2 g 6 g	For doses ≤ 4 g, use 2-g vial For doses > 4 g, use 6-g vial
Ceftriaxone	1 g 10 g	For doses ≤ 10 g, use 1-g vial For doses > 10 g, use 10-g vial
Cefuroxime	1.5 g 7.5 g	For doses ≤ 7.5 g, use 1.5-g vial For doses > 7.5 g, use 7.5-g vial

[a] This table lists only some examples from the complete list of drugs.
[b] This column shows the commercial vial sizes available for each drug.
[c] Choice of vial size is determined according to the total amount of drug required at the time of drug preparation.

from 597 mL in Wastage Study 1 to 1317 mL in Wastage Study 2. This increase of 720 mL in weekly wastage represents a 120% increase in total amount wasted. However, this increase appears to be partially offset by optimization of use of different vial sizes. Specifically, the mean volume wasted in Wastage Study 3 was 1110 mL, which represents only a 513-mL (86%) increase relative to Wastage Study 1.

What is promising is the apparent 34% reduction in waste from Wastage Study 2 to Wastage Study 3, following optimization of use of different vial sizes in combination with the new BUD guidelines. It is important to note that implementation of the updated BUD guidelines and vial-size optimization each represent a change to the pharmacy technicians' routine duties. Although the research team was trained on the study protocol, we did not supervise the technicians in the sterile compounding clean room, and we were not able to build the vial optimization protocols into our electronic records. As a result, there may have been technician errors causing wastage (due to the novelty of the procedures and individual technique), as well as changes in workflow relating to the study protocol. Furthermore, it was not possible to optimize utilization of all vial sizes. Some larger vials were used for compounded sterile products despite the recipe requiring a smaller volume. Also, the reconstituted vials used for compounded sterile product recipes were collected, which caused some overestimation of wastage. Taken together, however, these data show that although wastage numbers were still higher under the 2016 BUD parameters, the employment of simple strategies to optimize the use of different vial sizes allowed us to bring actual wastage volumes down by approximately 34%.

ALGORITHMIC WASTAGE PREDICTIONS MONTH-OVER-MONTH AND ASSOCIATED COSTS

To investigate whether the results from the 3 wastage studies were in agreement with monthly predictions of the volume of wasted drugs, we performed mathematical estimations of the wastage in each vial to generate monthly wastage estimates. Specifically, we used a monthly report produced from the electronic medical record—the Dispense Workload Report—to mathematically predict the volume of wastage and associated costs due to discarded vials from August 2018 to July 2019. The raw data from the reports were submitted to an algorithm in a Visual Basic application (Microsoft Corporation) to calculate the volume of waste from every vial according to the required dose for each drug (Table 3). This process allowed us to calculate the volume wasted and the cost of this wastage for each drug over a 1-year period under 3 different study conditions: before implementation of the 6-h BUD; after implementation of the 6-h BUD; and after vial-size optimization. In the analysis, we considered only dispensed doses directly extracted from vials for the drugs presented in Appendix 3.

The algorithm for wastage calculation before implementation of the 6-h BUD was built on the following assumptions: (1) vials were considered to have been discarded if either the vial's expiry date had passed or the remaining volume was insufficient to prepare a full dose; (2) doses were compounded in the exact order of the data report (i.e., doses dispensed at the same time were not rearranged to reduce the number of vials); (3) when a new vial of a drug was opened, the previous vial of this drug was discarded; (4) the vial size attributed to each drug was always the same; and (5) when the BUD was reached and a dose was required, the dose was delivered before the vial was discarded. The algorithm for calculation of wastage after implementation of the 6-h BUD was built on the basis of the same assumptions, with the exception that the BUD was reduced to 6 h or less if the manufacturer's BUD was shorter. The algorithm after vial-size optimization used the same assumptions, with the addition of the consideration of vial size. Wasted volumes were slightly overestimated to account for the volume remaining in the vials on the last day of the month; this overestimation is less when the BUD is 6 h.

The performance of the algorithm was assessed by comparing the predicted results with the corresponding extrapolation for the month of the wastage audit. The observed difference in the results for the prediction compared with the extrapolation was likely due to differing work practices of the various pharmacy technicians performing the sterile

TABLE 3. Algorithmic Prediction of Volume of Wastage and Associated Costs

Year and Month	Condition; Predicted Volume Wasted (mL)			Condition; Cost of Wastage ($CAD)		
	With Manufacturer BUD	With 6-h BUD	With Optimal Use of Vial Sizes	With Manufacturer BUD	With 6-h BUD	With Optimal Use of Vial Sizes
2018						
August	20 105	32 627	11 775	6 366	9 870	4 660
September	19 306	32 401	10 026	7 410	11 671	1 966
October	11 951	23 612	10 424	7 908	12 439	1 463
November	13 405	24 963	11 161	7 322	9 933	1 968
December	11 381	22 620	9 487	6 890	9 396	2 661
2019						
January	23 810	35 971	13 302	6 799	9 954	3 522
February	11 849	20 798	10 125	4 459	5 960	3 915
March	10 854	23 333	8 655	5 213	7 645	3 798
April	13 746	24 174	10 101	4 507	7 081	5 437
May	18 123	27 964	9 642	5 654	7 725	6 560
June	9 844	22 007	10 842	6 228	8 646	4 515
July	12 376	24 005	10 387	5 813	8 916	4 320
Mean	14 729	26 206	10 494	6 214	9 103	3 732
SD	4 454	4 892	1 196	1 121	1 850	1 517

BUD = beyond-use date, SD = standard deviation.

compounding (depending on their ability to adapt to new procedures in a short time without any failures of technique). It is important to note that applying vial-size optimization to a greater number of drugs, as well as to recipes for compounded sterile products, would further increase cost savings. Furthermore, although there was significant overlap in the drugs used for the 3 wastage studies reported here (see Appendixes 1, 2, and 3, respectively), some drugs appeared in just one study and were absent from the others (e.g., naloxone was considered only in Wastage Study 1, gentamicin was considered only in Wastage Study 2, and caspofungin was considered only in Wastage Study 3). An additional study could be performed with heightened control of the sterile compounding of the drugs, as well as a fixed list of drugs used for both the actual and the algorithmic calculations. Such a study would allow more rigorous comparisons and would improve intertester variability of the wastage measurement, serving to reduce the observed difference between actual and extrapolated values.

In a comparison of predicted wastage according to the manufacturer's BUD with predicted wastage after implementation of the new 6-h BUD, it was determined that the mean predicted total monthly wastage increased from 14 729 mL before implementation of the new 6-h BUD (i.e., manufacturers' BUD) to 26 206 mL after implementation, reflecting an increase in volume of wastage of approximately 78%. In a comparison of predicted wastage according to the manufacturer's BUD with predicted wastage after optimization of use of different vial sizes, the mean predicted total monthly wastage was 10 494 mL, a decrease of 29%. Similarly, there was a 60% decrease in wastage when predicted monthly wastage was compared between the new 6-h BUD and the optimized use of different vial sizes (26 206 mL and 10 494 mL, respectively).

In terms of changes in associated costs (Table 3), the algorithm predicted that the yearly cost of increased wastage caused by implementing the 6-h BUD would be $34 668 (i.e., mean monthly increase of $2889 × 12 months), a 46% increase. However, optimization of use of different vial sizes resulted in an estimated yearly saving of $29 784 (i.e., mean monthly decrease of $2482 × 12 months), despite the need to comply with BUD requirements. These mathematical analyses show that under predicted conditions of optimization of the use of available vial sizes, overall wastage of drugs and resultant costs can be notably reduced month-over-month.

IMPLICATIONS AND SIGNIFICANCE FOR PRACTICE

Implementation of the updated 6-h BUD guidelines in the central IV admixture clean room of the CHEO pharmacy caused an increase in drug wastage. Specifically, there was a 120% increase in the volume of wastage measured from Wastage Study 1 to Wastage Study 2. However, by employing simple strategies to optimize use of available vial sizes, we were able to reduce wastage volumes by approximately 34% (although wastage still remained higher than before implementation of the new BUD guidelines). Furthermore, our algorithm

predicted that by optimizing the use of different vial sizes, we could generate total savings, year over year, of $29 784. In our effort to develop cost-reduction methods that are in compliance with good manufacturing practices, we found that an increase in wastage could be mitigated by optimizing the use of various vial sizes. Our prediction models indicate that vial-size optimization will more than offset the additional cost of wastage due to the 6-h BUD. However, in practice, at least when vial-size optimization programs are newly introduced, these savings will likely not be fully realized, since it takes time for staff to become familiar and gain practice with the best way to optimize use of different vial sizes. Reinforcement of optimization practices with technicians, along with continued monitoring, will help in fully realizing cost savings.

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Pénuries de médicaments au Canada au cours des 24 derniers mois : la situation ne fait que qu'empirer

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INTRODUCTION

Le marché canadien du médicament est au cœur de l'actualité américaine avec la volonté du président Trump et de la Maison-Blanche de favoriser l'importation massive de médicaments provenant du Canada afin de réduire les coûts d'acquisition de ces produits pour les patients américains[1].

Shepherd a publié en 2010 une étude modélisant l'impact d'une importation américaine éventuelle de médicaments provenant du Canada. Dans l'hypothèse où 10 à 20 % des ordonnances du marché américain seraient honorées par des médicaments provenant du Canada[2], l'auteur a estimé que les réserves canadiennes de médicaments seraient épuisées respectivement en 268 et 201 jours. Une mise à jour de cette modélisation publiée en 2019 indique que les stocks canadiens seraient épuisés en 118 jours[3]. Dans une déclaration à Global News en décembre 2019, Alexander Cohen, alors porte-parole de la ministre de la Santé du Canada, a indiqué que le gouvernement protégera l'approvisionnement et l'accès aux médicaments sur lesquels les Canadiens comptent[4].

Indépendamment de cette menace, le Canada fait déjà face à de nombreuses pénuries de médicaments au quotidien, en dépit d'une déclaration obligatoire de pénuries réelles ou anticipées imposée aux fabricants canadiens depuis 2017[5]. Plusieurs auteurs ont étudié la problématique des pénuries de médicaments au Canada[6-13]. Ces pénuries sont liées à de nombreuses raisons, dont des pénuries de matière première de médicaments et de fournitures associées à la production de médicaments, des problèmes de fabrication, des enjeux réglementaires liés à la conformité des lieux de production, des modalités de remboursement, etc.[6,7]. Malgré ces efforts législatifs et plusieurs consultations sur le sujet[14], la situation semble se détériorer.

Nous nous sommes donc intéressés à l'état des pénuries de médicaments au Canada et en particulier à celles vécues en établissement de santé.

MÉTHODES

Il s'agit d'une étude descriptive et rétrospective. L'objectif principal est de décrire les pénuries de médicaments au Canada. L'étude porte sur les données de pénuries de médicaments sur une période de 24 mois, soit du 4 septembre 2017 au 31 août 2019.

Deux sources de données ont servi à décrire l'état des pénuries, soit le site canadien de déclaration obligatoire (penuriesdemedicamentscanada.ca) de l'ensemble des pénuries sur le marché canadien et la liste hebdomadaire du grossiste McKesson Canada pour les pénuries ciblant le marché canadien hospitalier. McKesson Canada, un grossiste de médicaments qui compte 13 centres de distribution répartis dans sept provinces canadiennes, transmet cette liste par courriel à tous les membres du groupe d'approvisionnement en commun SigmaSanté en vertu d'une obligation contractuelle. La liste contient tous les médicaments à contrat en pénurie chez le grossiste, les médicaments retirés du marché et les médicaments dont la pénurie est résolue.

Aux fins de cette étude, un épisode de pénurie de médicaments est défini comme un produit non disponible. La définition d'un produit porte sur sa dénomination commerciale, sa teneur, sa forme, sa quantité et son fabricant (p. ex. Apo-naproxène, 500 mg, comprimé, boîte de 100 comprimés, Apotex).

Des deux sources de données consultées, nous avons extrait l'ensemble des produits en pénurie. Les données extraites de chaque source de données ont été regroupées dans deux chiffriers distincts (Excel, Microsoft Corporation) puis traitées afin d'éliminer les doublons et d'établir, pour chaque produit, une date de début et de fin de pénurie. À partir des données recueillies, nous avons ajouté manuellement le statut du produit (c.-à-d. innovant ou générique) et la voie d'administration (c.-à-d. entéral ou parentéral). Afin de calculer la durée médiane des épisodes de pénurie, à la fin

de la période d'extraction des données, nous avons attribué arbitrairement aux pénuries non résolues la date de fin de pénurie du 31 août 2019. Dans le cas où le laps de temps entre deux épisodes successifs de pénurie était inférieur à 30 jours, la pénurie était considérée comme unique et continue. Dans le cas contraire, nous avons conclu à deux épisodes distincts de pénurie.

Pour chaque épisode de pénurie, nous avons relevé la dénomination commune et commerciale du produit, y compris la teneur, la forme, le format, le statut du produit (c.-à-d. innovant ou générique), la classe thérapeutique (selon la classification de l'American Hospital Formulary Service indiquée dans la base de données sur les produits pharmaceutiques de Santé Canada) et la voie d'administration (c.-à-d. parentérale ou entérale), la date de début de l'épisode, la date de fin de l'épisode et le fabricant.

Afin de décrire les pénuries, nous avons calculé le nombre d'épisodes de pénurie de médicaments, le nombre de fabricants ayant au moins un produit en pénurie, la durée des épisodes de pénurie, la proportion des épisodes de pénurie provenant de produits génériques (c.-à-d. le produit est un médicament générique même s'il est désormais le seul disponible sur le marché en cas de retrait du médicament innovant) et la proportion des épisodes de pénurie de médicaments destinés à la voie parentérale. De plus, nous avons calculé la proportion des épisodes de pénurie de médicaments par fabricant.

Seules des statistiques descriptives ont été effectuées.

RÉSULTATS

Le tableau 1 présente un profil des épisodes de pénurie de médicaments sur une période de 24 mois, soit du 4 septembre 2017 au 31 août 2019.

La proportion par ordre décroissant des 10 épisodes de pénurie les plus importants par fabricant et par source de données consultée (c.-à-d. site canadien *vs* McKesson Canada) est la suivante : Apotex (16,9 % *vs* 12,6 %), Pharmascience (11,4 % *vs* 10,1 %), Sandoz (7,7 % *vs* 4,5 %), Teva (6,49 % *vs* 21 %), Mylan (3,57 % *vs* 2,9 %), Pfizer (3,3 % *vs* 6,6 %), Sivem (3,2 % *vs* 0 %), Pro Doc (2,9 % *vs* 0 %), Marcan (2,6 % *vs* < 1,4 %) et Merck (2,6 % *vs* 0,7 %).

Dans le site canadien, les fabricants peuvent indiquer le motif de la pénurie. À partir des données extraites, les raisons évoquées par ordre décroissant d'importance étaient : perturbation de la fabrication du médicament (55,4 %), retard dans l'expédition du médicament (17 %), augmentation de la demande du médicament (11,3 %), autres raisons non précisées (9,9 %), exigences liées au respect des bonnes pratiques de fabrication (3,9 %), pénurie d'un ingrédient actif (2,1 %) et pénurie d'un ingrédient ou composant inactif (0,6 %).

Le tableau 2 présente un profil des épisodes de pénurie de médicaments par classe thérapeutique. Le tableau présente les proportions des données du site canadien par ordre décroissant d'importance.

DISCUSSION

Cette étude descriptive présente les données les plus récentes de l'état des pénuries de médicaments au Canada.

Nous avons calculé respectivement 6948 et 1379 épisodes de pénurie de médicaments en 24 mois, soit de 2017 à 2019, selon le site canadien et selon les données d'un grossiste canadien pour les établissements de santé (McKesson Canada). Le nombre d'épisodes est 4,7 fois plus élevé sur le marché canadien que chez le grossiste. Ceci n'est pas étonnant, étant donné que tous les produits utilisés à l'échelle du pays concernent la pratique en milieux communautaire et hospitalier. De plus, le nombre d'épisodes de pénurie de médicaments est plus élevé en 2017-2019 qu'en 2016-2017 avec une hausse moyenne de 63 % (de 2129 à 3474 épisodes / période de 12 mois) selon les données du site canadien et de 18 % (de 583 à 690/période de 12 mois) selon les données de McKesson Canada[6]. Ces données confirment les résultats de l'enquête menée auprès des pharmaciens canadiens à l'automne 2018 à l'effet que les pénuries de médicaments auraient subjectivement augmenté au cours des trois à cinq dernières années[15].

TABLEAU 1. Profil des épisodes de pénurie de médicaments sur une période de 24 mois, soit du 4 septembre 2017 au 31 août 2019

Variable	Selon site canadien penuriesdemedicamentscanada.ca (2017–2019)	Selon grossiste McKesson Canada pour SigmaSanté (2017–2019)
Nombre d'épisodes de pénurie de médicaments	6948	1379
Nombre de fabricants avec au moins un produit en pénurie	132	70
Durée des épisodes de pénurie en jours (médiane [min, max])	86,5 [1, 4799]	109 [2, 1562]
Proportion des épisodes de pénurie provenant de produits génériques	79,2 %	85,7 %
Proportion des épisodes de pénurie de produits destinés à la voie parentérale	14,7 %	27 %

Notre étude montre que le nombre de fabricants ayant au moins un produit en pénurie était de 132 selon le site canadien et de 70 d'après les données du grossiste. Le nombre de fabricants est donc plus élevé que celui observé en 2016-2017 (68 *vs* 43)[6]. Bien que des fusions aient été observées dans le domaine pharmaceutique au cours des dernières années, ce qui consolide le nombre de joueurs sur le marché du médicament, de nouveaux fabricants, tant de médicaments innovants que génériques, voient périodiquement le jour.

Le site canadien et les données du grossiste révèlent respectivement une durée médiane des épisodes de pénuries de 86,5 et de 109 jours, en légère hausse par rapport aux données de 2016-2017 (85 et 93 jours)[6]. Les proportions d'épisodes de pénurie provenant de produits génériques demeurent inchangées (79,2 % et 85,7 % en 2017-2019 *vs* 80,7 % et 84,9 % en 2016-2017) tout comme les proportions d'épisodes de pénurie de produits destinés à la voie parentérale (14,7 % et 27 % en 2017-2019 *vs* 14 % et 25,9 % en 2016-2017). De même, les proportions d'épisodes de pénurie de médicaments par classe thérapeutique ont peu changé depuis la dernière étude[6].

Dans un rapport de 124 pages de la Food and Drug Administration (FDA) publié en 2019, trois causes majeures liées aux pénuries de médicaments ont été déterminées : 1) il y a une absence d'incitatifs à la production de médicaments moins rentables (p. ex. injectables génériques), 2) le marché ne reconnait ni ne récompense les fabricants qui ont un système mature de gestion de la qualité de leurs

TABLEAU 2. Profil des épisodes de pénurie de médicaments par classe thérapeutique

	Source des données : % des épisodes de pénurie	
Classe thérapeutique	Site canadien penuriesdemedicamentscanada.ca, 2017–2019 (*n* = 6948)	Grossiste McKesson Canada pour SigmaSanté, 2017–2019 (*n* = 1379)
Système nerveux central (28:00)	28,12	21,39
Cardiovasculaires (24:00)	22,37	14,50
Anti-infectieux (08:00)	8,33	9,64
Gastro-intestinaux (56:00)	5,25	5,95
Électrolytes-diurétiques (40:00)	4,84	4,86
Autres médicaments (92:00)	4,76	8,63
Hormones et substituts (68:00)	4,69	5,73
Peau et muqueuses (84:00)	4,12	5,73
Antinéoplasiques (10:00)	3,90	5,73
Oto-Rhino-Laryngo-Ophtalmo (52:00)	3,37	4,50
Système nerveux autonome (12:00)	3,04	3,84
Agents immunisants (80:00)	1,24	0
Anesthésiques locaux (72:00)	1,22	2,25
Médicaments du sang (20:00)	1,19	2,25
Spasmolytiques (86:00)	1,08	1,45
Antitussifs, expectorants et agents mucolytiques (48:00)	0,85	0,44
Vitamines (88:00)	0,46	1,67
Agents diagnostiques (36:00)	0,45	0,22
Antihistaminiques (4:00)	0,30	0,44
Antidotes des métaux lourds (64:00)	0,19	0
Sels d'or (60:00)	0,12	0,07
Ocytociques (76:00)	0,07	0,22
Enzymes (44:00)	0,04	0

opérations, et 3) les défis logistiques et réglementaires compliquent la tâche des parties prenantes pour un retour à la normale à la suite d'une pénurie[16]. La FDA formule trois recommandations clés : 1) développer une compréhension commune de l'impact des pénuries de médicaments et préciser les pratiques contractuelles qui peuvent y contribuer (cette recommandation comporte trois sous-éléments soit [a] quantifier les méfaits des pénuries de médicaments, en particulier ceux qui mènent à une détérioration dela santé des patients et à une augmentation des coûts pour les fournisseurs de soins de santé, [b] assurer une meilleure caractérisation des pénuries et [c] favoriser une plus grande transparence dans les pratiques contractuelles du secteur privé); 2) créer un système de notation pour inciter les fabricants de médicaments à investir pour atteindre la maturité du système de gestion de la qualité; et 3) promouvoir des contrats durables avec le secteur privé.

En outre, le rapport note que la plus grande proportion de produits finis disponibles sur le marché américain provient d'usines localisées le plus souvent outre-mer (p. ex. Inde [24 %], Europe [18 %], reste du monde [10 %], Chine [8 %]); 37 % des produits finis proviennent encore d'usines localisées aux É.-U. Nous ne disposons pas de données similaires pour le Canada, mais il semble urgent de réfléchir aux stratégies préservant notre souveraineté pharmaceutique et notre capacité à produire et à assurer des stocks adéquats et sécuritaires de médicaments pour tous les patients canadiens. Enfin, si la crise des pénuries est désormais un problème mondial, chaque pays doit déterminer des stratégies propres à son environnement juridique, industriel et professionnel[17].

Dans la foulée de ces recommandations, il semble urgent de réunir à nouveau les parties prenantes afin de définir les conditions gagnantes pour préserver la pérennité du marché pharmaceutique au Canada. À l'échelle des pharmaciens d'établissement, il est souhaitable de privilégier des stocks plus importants de tous les produits critiques (p. ex. pour au moins 90 jours) et de revoir les modalités contractuelles avec les groupes d'approvisionnement en commun.

Cette étude comporte des limites. Un épisode de pénurie ne signifie pas forcément que cette dénomination commune n'existe plus sur le marché, étant donné que les produits génériques sont souvent fabriqués par plus d'un fabricant. Toutefois, la pénurie d'un produit d'un fabricant donné génère des pénuries en cascade, affecte les achats effectués sur des bases contractuelles et augmente les risques d'erreurs médicamenteuses. De plus, l'étude ne permet pas d'évaluer les conséquences administratives et cliniques liées à ces pénuries.

CONCLUSION

Il y a de plus en plus de pénuries de médicaments au Canada, tant à l'échelle communautaire qu'hospitalière. Dans la foulée des recommandations de la FDA, il semble nécessaire de décrire et de caractériser davantage ces pénuries afin de limiter leur portée. Des efforts visant à organiser une concertation à l'échelle canadienne entre toutes les parties prenantes semblent également urgents.

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Subcutaneous Infusion of Pamidronate in a Hospice Patient with Hypercalcemia: A Case Report

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INTRODUCTION

Hypercalcemia is a complication of cancer, reported to affect between 10% and 40% of patients with cancer and occurring in those with both solid tumours and hematologic malignancies.[1-4] Cancer is the most common cause of hypercalcemia in the inpatient setting, most frequently breast, renal, and lung cancer and multiple myeloma.[1,2,5] Malignancy is usually clinically evident by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy often have a poor prognosis.[1]

There are several mechanisms by which hypercalcemia of malignancy can occur. The major mechanism, associated with approximately 80% of cases, is secretion of parathyroid hormone–related protein by the tumour.[1-4] Other mechanisms include local release of cytokines (including osteoclast-activating factors) from osteolytic metastatic lesions, tumour production of 1,25-dihydroxyvitamin D (calcitriol), and production or secretion of parathyroid hormone secondary to parathyroid carcinoma.[1,2,4]

For hypercalcemia and bone pain, IV administration of bisphosphonates is a recognized, first-line treatment option.[2-4] In our health authority, Fraser Health (located in the Lower Mainland of British Columbia), IV pamidronate is one of the first-line bisphosphonates in the treatment of hypercalcemia. However, for patients receiving palliative care in hospice settings, Fraser Health policy stipulates that IV administration is not an option because hospice nursing staff are not trained to provide the higher level of monitoring required with this route of administration. Additionally, other risks and barriers to IV administration in the palliative care population have been reported, including thrombophlebitis, pain secondary to needle insertion, difficult venous access, and infection.[6,7]

The subcutaneous (SC) administration of bisphosphonates for patients receiving palliative care has been reported as an alternative to IV administration.[6-8] To determine the feasibility of an alternative route of administration in our setting, we searched PubMed and Ovid MEDLINE using the terms "hypercalcemia", "bisphosphonates", and/or "injections, subcutaneous". This search identified the same 3 reports of SC administration of bisphosphonates in the palliative setting of which we were already aware[6-8]; no additional reports were found. Clodronate, a first-generation bisphosphonate, has been used in the palliative care setting in Edmonton, Alberta, with reported safety and efficacy.[7,8] Duncan[6] reported the SC use of pamidronate in a UK hospital, where the drug was administered to 10 patients, of whom 7 had a biochemical response, with serum calcium decreasing to within normal limits. However, although there is reported evidence for SC administration of clodronate, this drug is unavailable for use in our health authority, and although Duncan[6] reported biochemical response in 7 of 10 patients who received SC pamidronate, she did not discuss patients' symptoms or their symptomatic response. As such, evidence for and timing of symptomatic efficacy to guide SC administration of pamidronate is lacking from the literature at this time.

We report a case of hypercalcemia of malignancy in a patient who experienced biochemical and symptomatic response to pamidronate administered by the SC route.

CASE REPORT

A 70-year-old man with fungating inoperable penile carcinoma with lung and lymph node metastases did not wish to undergo further investigation or oncologic treatment.* The patient was transferred from an inpatient palliative care unit to hospice on August 31, 2018. He had a history of malignancy-related hypercalcemia, which had responded to IV administration of pamidronate on August 12, 2018 (before transfer to hospice). This was the first and only dose of pamidronate that the patient received, and there were

*The patient died prior to consent for publication being obtained, and repeated attempts to contact the substitute decision-maker were unsuccessful.

both biochemical (Table 1) and symptomatic (increased energy, decreased nausea and confusion) responses.

During hospice team rounds on September 12, it was reported that the patient was more confused than previously noted during this admission, being unable to follow simple directions. The patient was not oriented to place or time, was not eating or drinking, and was refusing his oral medications and routine care. A urine sample was sent for culture and sensitivity testing, which yielded no growth. No blood was drawn for culture, as per the patient's goals of care; the patient was afebrile. IV fluids were not initiated, as per hospice policy. There were no recent medication changes thought to be contributory to the patient's change in function, and the patient was not receiving calcium or vitamin D supplements. Routine blood tests were ordered, including serum calcium, albumin, and creatinine; the results of previous liver and kidney function tests at the inpatient palliative unit were within normal limits. Laboratory results on September 14 revealed that the patient had elevated serum calcium (Table 1).

Pamidronate 90 mg in 500 mL of 0.9% sodium chloride (normal saline) via SC infusion was started on September 18; the drug was infused over 24 h via gravity drip, similar to how hypodermoclysis is administered in our hospice units. Follow-up blood tests on September 26 showed a reduction of serum calcium to within the normal range (but no corresponding measurement of albumin was ordered at that time; see Table 1). In addition, the patient's symptoms resolved (return of appetite; alert and oriented to person, place, and time; and taking oral medications) within 24 h of completing the infusion. Notably, for the patient's comfort during pamidronate administration, the infusion site was re-located from the upper arm to the abdomen.

DISCUSSION

Although there is substantial evidence supporting the use of IV bisphosphonates as first-line therapy for hypercalcemia of malignancy, there is limited literature showing evidence for the safety and efficacy of bisphosphonate administration via the SC route and nothing describing the kinetics of SC bisphosphonate. The most robust evidence for SC administration of bisphosphonate was detailed in a retrospective cohort study, in which Roemer-Bécuwe and others[7] reviewed the use of SC clodronate for management of hypercalcemia and/or bone pain in the palliative care population in Edmonton.[7] The 149 patients in that study received a total of 254 infusions over a 4-year period and were evaluated retrospectively for safety and efficacy of SC administration of clodronate. The reported toxic effects included pain (7.9% of infusions), swelling (3.1%), bruising (2.8%), redness (6%), and discharge (0.4%). The authors reported that local toxicity was mild, with discomfort being resolved by application of hot packs and discontinuation of the infusion, the latter being required for only 2 infusions (1.0%). Of the 90 infusions administered for hypercalcemia management, only 43 met the criteria for evaluation of efficacy (because of missing data), with 32 (74.4%) achieving normalization within 5 days, 3 (7.0%) during week 2 after the infusion, and 8 (18.6%) having no decrease in calcium. The authors reported a significant overall decrease in calcium levels ($p < 0.0001$) within 5 days after SC clodronate infusion. Although this cohort study provided evidence for the safety and efficacy of clodronate for management of hypercalcemia of malignancy,[7] this drug is not available for use in Fraser Health and could not be considered as an option for management in our patient. However, the same study was considered to provide evidence for use of bisphosphonate therapy through the SC route of administration in the palliative care population, which provided a rationale to consider use of another drug, pamidronate, via the SC route.

In a case series report, Duncan[6] described the SC administration of pamidronate to 10 patients; for each patient 90 mg of drug was diluted in 375 to 1000 mL of normal saline and administered via an SC butterfly needle over 4 to 24 h. All of the patients had cancer at one of the

TABLE 1. Laboratory Results for Hospice Patient with Hypercalcemia[a]

Date	Serum Calcium (mmol/L)	Albumin (g/L)	Ionized Calcium (mmol/L)	Corrected Calcium (mmol/L)
Normal range	2.1–2.6	35–50	1.15–1.32	NA
August 11	Not ordered	21	1.79	NA
August 14	Not ordered	Not ordered	1.49	NA
August 17	1.99	17	Not ordered	2.57
September 14	3.48	29	1.91	3.7
September 26	2.18	Not ordered	Not ordered	NA

NA = not applicable/not available.

[a]Pamidronate was administered by the IV route on August 12 in the inpatient palliative care unit. The patient was transferred to hospice care on August 31 and received pamidronate by the SC route on September 18.

following sites: breast (n = 4), pancreas (n = 1), lung (n = 1), myeloma (n = 1), prostate (n = 1), and unknown primary origin (n = 2). Biochemical response, defined as reduction of serum calcium to within normal limits, occurred in 7 of the 10 patients. Inflammation of the SC sites was the most common adverse event and appeared more likely with quicker infusions, over 4 to 5 h; inflammation was less pronounced with longer infusions, over 12 to 24 h. Only 1 patient did not tolerate the infusion because of painful stinging. Unfortunately, there was no description of patients' symptomatic responses in this case series.

Denosumab is another SC treatment option for hypercalcemia of malignancy[9]; however, this drug was not considered in our case because the contracted pharmacy did not routinely stock it, and the acquisition delay (> 24 h) was thought to be unacceptable. In addition, the cost (approximately $600) would be covered by the BC Cancer Agency only if the patient were registered with the agency; the patient in our case was not registered (based on his goals of care and his desire not to receive any cancer-specific treatment), and the pharmacy therefore had no way of recouping its costs. The prescriber had previously used SC pamidronate for another patient; on the basis of this experience, combined with the reasons outlined above, we proceeded with this treatment option.

This case and previous cases reported in the literature indicate that SC pamidronate infusion is both well tolerated and worthwhile in the palliative care setting. Greater-than-usual dilution and a slower infusion rate add to the tolerability of administration of the drug by the SC route and represent a reasonable option for the treatment of hypercalcemia in Fraser Health hospices. We recommend that pamidronate 90 mg be diluted in 500 mL of normal saline and administered via SC infusion over 24 h (similar to how we administer hypodermoclysis in our hospice units), as the larger volume of fluid is also of benefit for patients with hypercalcemia. Patients should be monitored for infusion-site reactions (e.g., redness), and the SC infusion is likely best sited in the abdomen (as per the prescriber's previous experience with hypodermoclysis) where the infusion volume might be best tolerated; other potential sites include the thigh or the chest. The patient described here experienced only mild discomfort at the initial injection site, and this pain resolved once the infusion was re-sited to the abdomen.

CONCLUSION

In this case, pamidronate SC was safe and efficacious for treatment of the patient's hypercalcemia of malignancy. This case furthers our knowledge of how best to administer pamidronate by this route, with regard to fluid volume, rate of infusion, and infusion site.

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Successful Transition from High-Dose Methadone to Buprenorphine via Microdosing in the Outpatient Setting: A Case Report

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INTRODUCTION

Transitioning from full μ-receptor agonists, such as methadone, to buprenorphine can be challenging because of the potential for precipitated withdrawal.[1] Buprenorphine is a partial μ-receptor agonist and has lower intrinsic activity at μ receptors than methadone and other full μ-receptor agonists.[2] Because of its high affinity for μ receptors, buprenorphine replaces methadone and results in precipitated withdrawal.[2] Conventionally, to make the transition to buprenorphine, the methadone dose had to be gradually tapered, to 30 mg daily, and then stopped, followed by induction of buprenorphine 36 to 72 h later, once moderate opioid withdrawal symptoms were detected.[3] Not only is this conventional technique time-consuming, but it also puts clients at risk of relapse and overdose due to the extended period of destabilization. Consequently, clinicians are searching for other novel approaches that decrease the extent of destabilization. One such method, known as the Bernese model, involves gradual upward titration of very small doses of buprenorphine while maintaining the same dose of methadone.[1] This method of titration results in a very gradual increase in the percentage of receptors occupied by buprenorphine while allowing the remaining μ receptors to interact with methadone.[1]

One common reason for transitioning from methadone to buprenorphine is concern about prolongation of the QT interval. The methadone formulations available in Canada are racemic mixtures with propensity to increase corrected QT interval (QTc) in a dose-dependent fashion.[4] It has been shown that the (*S*)-enantiomer of methadone (dextromethadone) is the cause of this dose-related adverse effect.[5] Prolongation of the QTc interval is a marker of the impending possibility of torsade des pointes and sudden death. The risk of sudden cardiac death increases 4-fold when QTc is 500 ms or longer.[6]

Buprenorphine has been shown to be as effective as methadone in suppressing illicit opioid use, though perhaps slightly less effective in terms of patients remaining in treatment.[7] Furthermore, when taken as recommended, buprenorphine currently is not known to potentiate the risk of torsade des pointes,[8] and it is considered first-line treatment for opioid use disorder because of its safety profile.[9]

There is no specific guideline for the interval of dosing or speed of titration to be used in buprenorphine microdosing, and the published evidence to date consists only of case series.[1,10] To contribute to the available literature, we present a case of transition from methadone to buprenorphine by the Bernese method, in the outpatient setting, in a patient with acquired QTc prolongation. The sublingual formulation of buprenorphine used in this case was combined with an opioid antagonist, naloxone, which is not absorbed sublingually. This combination is designed to discourage abuse of buprenorphine, as naloxone can precipitate withdrawal symptoms in patients with opioid use disorder.[3]

CASE REPORT

A 29-year-old man with a long history of opioid use disorder, who had been receiving methadone for more than 5 years, was transferred to our outpatient clinic; the daily dose at the time of transfer was 160 mg orally.* His past medical history was significant for depression and anxiety; however, he was not receiving any other medications or supplements at the time of transfer. Secondary to continuous illicit opioid use, the methadone dose was gradually increased to 220 mg daily.

Upon the performance of electrocardiography (ECG), as part of regular annual care, it was noted that QTc was prolonged, at 502 ms; previous ECG 2 years earlier had shown QTc of 464 ms. The dose of methadone was reduced while Holter monitoring and echocardiography were performed, for which the results were normal. After we reviewed potential risks and benefits with the client, he informed us that his wish was to

*The client provided written informed consent for publication of this report.

use buprenorphine/naloxone instead of methadone. Different approaches to transitioning from methadone to buprenorphine/naloxone were described, and the client expressed interest in pursuing the microdosing (Bernese) method.

At the time of initiation of buprenorphine/naloxone, in November 2018, the client was receiving 200 mg of methadone daily. The combination product was initiated at 0.5 mg of buprenorphine and 0.125 mg of naloxone daily, and the client did not report any withdrawal symptoms. Buprenorphine/naloxone was increased to 1/0.25 mg daily after 5 days, and the dose was then increased by 1/0.25 mg weekly until the dose of 8/2 mg daily was reached. Concurrently, the methadone dose was decreased by 10 mg weekly. As such, after 8 weeks of therapy (in early 2019), the client was receiving 8 mg of buprenorphine, 2 mg of naloxone (in combination), and 110 mg of methadone daily.

At that time, the client moved to a recovery program, with care being managed by another provider. When he returned to our care, he was receiving 22 mg buprenorphine, 5.5 mg naloxone (in combination), and 90 mg methadone daily. From that point, we slowly increased the buprenorphine/naloxone dose (by 2/0.5 mg every few days) and very quickly decreased his methadone dose from 90 mg to zero (Figure 1). The optimal maintenance dose of buprenorphine/naloxone should be able to suppress physical withdrawal signs and symptoms. It also should enable the patient to cease illicit opioid use. Consequently, the buprenorphine/naloxone dose needed to achieve these goals will differ from one person to another.[2] In this case, titration up to 32/8 mg of buprenorphine/naloxone daily was elected, as per the client's preference. The client consistently reported fewer psychological cravings at higher doses.

Psychological and physical withdrawal symptoms were assessed during interactions at clinic visits and through client self-reporting. There were no documented physical withdrawal scales available for us to report. The client did not exhibit or report any physical withdrawal symptoms during the buprenorphine/naloxone initiation or methadone tapering. Furthermore, while under our care, the results of all urine drug screening during clinic visits were negative for illicit opioids. Follow-up ECG 2 weeks after discontinuation of methadone indicated QTc of 373 ms.

DISCUSSION

In this case report, we have described buprenorphine/naloxone microdosing for a client who was receiving 220 mg of methadone daily. The reason for switching from methadone to buprenorphine/naloxone was QTc prolongation. Considering the current lack of guidelines for switching from high-dose methadone to buprenorphine/naloxone, our experience supports the concept of using an appropriate microdosing schedule to safely switch motivated clients from high-dose methadone to buprenorphine/naloxone. Starting the buprenorphine/naloxone at 0.5/0.125 mg daily and increasing the dose slowly made it possible to accomplish induction successfully. Tapering of the methadone dose is not required before initiation of buprenorphine/naloxone microdosing[10]; however, to ensure that we had taken appropriate actions to prevent risks related to QTc prolongation, we started reducing the methadone dose even before starting buprenorphine/naloxone. This case is unique in that methadone and buprenorphine/naloxone were taken simultaneously for an extended period, partly because of an

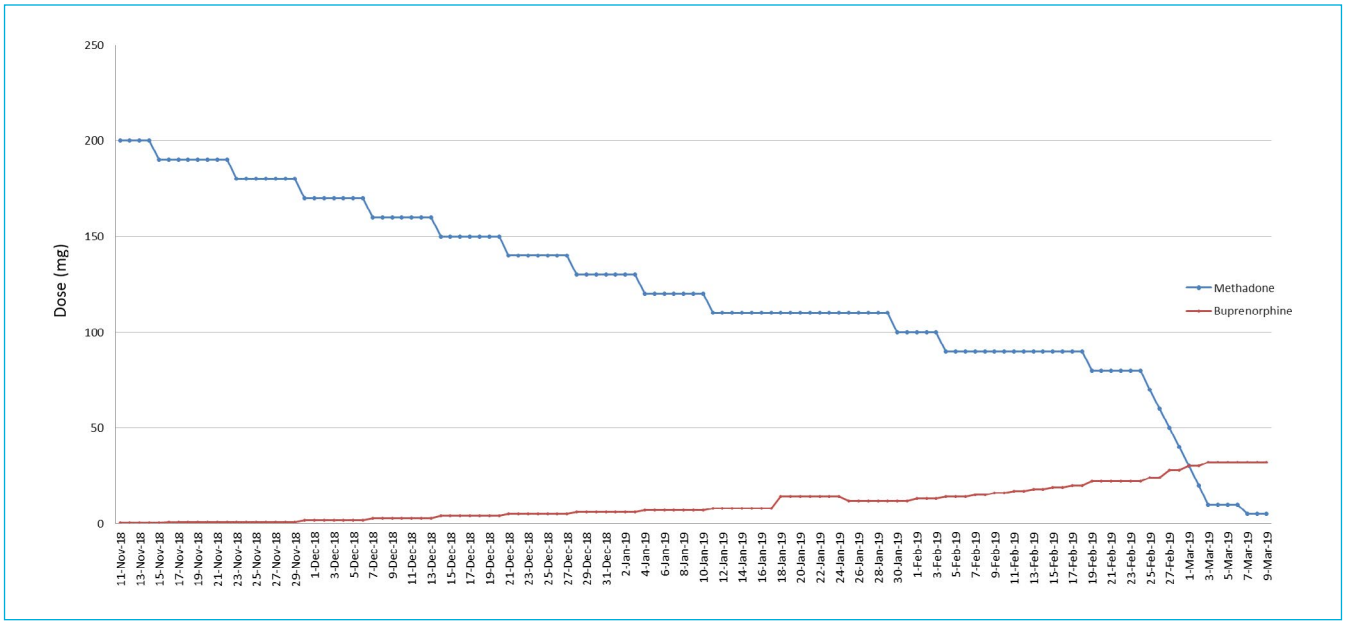

FIGURE 1. Time course of induction of buprenorphine/naloxone by microdosing (with data shown only for the buprenorphine component of the combination product) and tapering of methadone.

interruption in care and partly because of the client's anxiety about discontinuing methadone too quickly. However, no serious incident or adverse effects resulted from the simultaneous administration.

We recommend that any care plan should consider all potential changes to clients' living conditions, baseline functioning, and social stability. It must also be communicated to clients whose therapy is being transitioned to buprenorphine/naloxone that they will need regular, more frequent assessment. Such an approach provides an opportunity to promptly deal with adverse events and anxiety related to medication changes, which could improve adherence to the microdosing plan.

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Canadian Society of Hospital Pharmacists

Société canadienne des pharmaciens d'hôpitaux

Quelques mots sur mon association

par Zack Dumont

Les autres agents présidentiels et directrices générales, Jody Ciufo, et moi avons entamé un dialogue avec nos membres sous forme de forums de discussion. Nous avons reçu des commentaires constructifs, abordé des préoccupations, répondu à des questions et nous en avons aussi posé. Parmi celles-ci : « Que signifie pour vous la Société canadienne des pharmaciens d'hôpitaux (SCPH)? ». Pour moi, la réponse est simple : la SCPH est et sera toujours ma communauté. Bien que la diversité de pensée soit importante à mes yeux, j'ai été heureux de constater que beaucoup partageaient ce point de vue, puisque le mot « communauté » est celui qui est ressorti le plus souvent.

J'admire cette communauté depuis plus de 12 ans, lorsque j'étais encore étudiant. Lors des réunions et des activités de la Société, je rêvais à la manière dont la SCPH avait vu le jour. J'imaginais, qu'autrefois, il y a plus de 70 ans, lorsque les leaders de la profession se réunissaient, ils disaient peut-être : « L'union fait la force. Et si nous nous rencontrions régulièrement? Et si nous nous inspirions un peu de ce que font nos collègues pour accomplir certaines tâches sur notre lieu de travail? Et si nous nous réunissions à nouveau pour mettre en commun nos résultats? » Ces interrogations sont certainement très réductrices, mais quelle que soit la manière dont tout cela s'est vraiment passé, j'aime la vitalité de ces novateurs qui ont su voir la possibilité de créer quelque chose — comme une coopérative — quand personne n'y avait pensé, quand personne ne prêtait attention à eux. Qu'est-ce qui les a poussés à agir ainsi? Ces dirigeants étaient non seulement animés d'une vision, mais ils avaient aussi les compétences pour la concrétiser.

Aujourd'hui, la SCPH est plus forte que jamais. Il me semble que ses membres ressentent cette énergie. La SCPH demeure votre Société, votre coopérative. Quand je dis « votre », je veux vraiment dire qu'elle est totalement vôtre. Ma responsabilité consiste simplement à la diriger au cours des prochaines années, mais elle ne cessera jamais d'être entre vos mains. Une autre personne me succèdera le moment venu. Entretemps, la Société reste votre lieu de rencontre. Notre communauté ne s'arrêtera jamais, dans la mesure où nous voulons qu'il en soit ainsi.

Qu'est-ce qui nous unit? Quel dénominateur commun nous donne l'impression d'être chez nous? Notre récent sondage nous éclaire. Les membres nous disent qu'ils sont très satisfaits de nos offres pédagogiques, de ce journal et de nos programmes de résidence. Pour moi, ces moyens font partie de nos mécanismes principaux de communication, de défense et de promotion de l'une de nos valeurs communes : œuvrer pour les patients, avec comme unique objectif l'amélioration de leur condition. Toutes les décisions de pharmacothérapie que nous prenons ou que nous soutenons, que ce soit de commencer, d'arrêter ou de modifier une thérapie, visent à améliorer la situation des patients.

Je me sens intégré dans la Société, car je peux y voir des leaders et des modèles qui remportent des prix, qui obtiennent des bourses et aussi parce que je me suis mêlé à eux lors des activités de la Société. La SCPH est un endroit incontournable. Elle m'a façonné; elle m'inspire de la fierté et je lui en suis reconnaissant. Au cours des prochaines années, je prévois démontrer ma gratitude en étoffant et en renforçant notre communauté : une communauté de diversité et d'inclusion. Je prévois aussi de me concentrer sur l'amélioration des résultats pour les patients.

Il ne s'agit là que de mon plan. Un leadership formel n'est peut-être pas fait pour vous. Je vous encourage cependant à vous engager dans votre association professionnelle. Une Société comme la SCPH est en effet plus grande que la somme de ses parties, et en tant que membre engagé, vous obtiendrez d'elle plus que vous ne pourrez lui offrir. Votre association professionnelle : une communauté qui mérite votre dévouement.

[Traduction par l'éditeur]

Zack Dumont, BSP, ACPR, M. S. (Pharm.), est président et agent de liaison interne de la Société canadienne des pharmaciens d'hôpitaux.

Talkin' 'bout My Association

Zack Dumont

Along with the other presidential officers and Chief Executive Officer, Jody Ciufo, we've gotten out in front of membership for 'town hall'-like sessions. We've received positive reinforcement, fielded concerns, answered questions and asked a few of our own. A question we've been asking is "What does the Canadian Society of Hospital Pharmacists (CSHP) mean to you?". For me, the answer is easy. CSHP has and always will be my community. Though I celebrate diversity of thought, I was happy to see I wasn't alone. Many others felt the same, and we've got the word clouds to prove it.

I've admired this community since I was a student over 12 years ago. At Society meetings and events, I've had baseless daydreams about how CSHP came to be. I've imagined that way back when (more than 70 years ago!) leaders in the profession congregated, they said "Hey, there's probably strength in numbers. What if we got together regularly? What if we did some of the same things at our workplaces when we part? And then, what if we got together again and shared our findings?" Probably an over-simplification. Despite how it really happened, I enjoy the wholesomeness in these folks seeing an opportunity to form something—like a co-op—when no one gave that direction; no one was looking out for them. What compelled them to do that? These leaders had vision and, subsequently, the leadership skills to make it happen.

CSHP surges on today. I get the sense that members are feeling the energy. It remains your Society, your co-operative. And I mean 'your' entirely. I have the challenge to help shepherd it over the next few years, but it never stops being yours. After I'm done, someone else gets a turn. All the while, your meeting place goes on. Your community never stops, so long as we will it to carry on.

What ties us together? What common thread makes this feel like home? Our recent member survey provides some insight. Members tell us they are most highly satisfied with our educational offerings, this Journal, and residency programs. For me, these represent some of our main mechanisms for communicating, celebrating, and fostering one of our shared values: to work with patients, where the sole focus is to improve their outcomes. Knowing that whatever medication therapy decisions we make or support others to make—to start, stop, or change therapy—they have everything to do with improving patients' outcomes.

I feel included in the Society because I have seen leaders—role models—on display, winning awards, achieving fellowship, and because I have walked amongst them at Society events. CSHP is the place to be. It shaped me, it brings me pride, and for that I am grateful. My plan is to devote these next few years to demonstrating my gratitude by growing and strengthening our community, one of diversity and inclusion, and to focus on improving patient outcomes.

This is only my plan. Perhaps formal leadership is not for you. However, I encourage you to engage in your professional association. A society like CSHP is indeed greater than the sum of its parts, and, as such, you will get more from it than you can possibly give. Your professional association: a community worth devotion.

Zack Dumont, BSP, ACPR, MS(Pharm), is President and Internal Liaison for the Canadian Society of Hospital Pharmacists.

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