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The Canadian Journal of Hospital Pharmacy
Vol. 73, No. 4, Fall 2020
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Le Journal canadien de la pharmacie hospitalière
Vol. 73, nº 4, Automne 2020
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Address all correspondence concerning the journal to / Adressez toute correspondance concernant le journal à :
CJHP/JCPH
c/o Canadian Society of Hospital Pharmacists / Société canadienne des pharmaciens d'hôpitaux
30 porte Concourse Gate
Unit/unité 3
Ottawa ON K2E 7V7
Tel: 613.736.9733
Fax: 613.736.5660

For journal content inquiries / Pour les questions concernant le contenu
Stephen Shalansky
Editor/Rédacteur en chef
ext. / poste 228
e-mail: publications@cshp.ca

For article submissions / Pour la soumission d'articles
http://cjhp.msubmit.net

For journal administration and subscriptions / Pour l'administration du journal et les abonnements
Content Officer / Agente du contenu
ext. / poste 228

CJHP MISSION

The *CJHP* is an academic journal that focuses on how pharmacists in hospitals and other collaborative health care settings optimize safe and effective drug use for patients in Canada and throughout the world.

CJHP VISION

The aim of the *CJHP* is to be a respected international publication serving as a major venue for dissemination of information related to patient-centred pharmacy practice in hospitals and other collaborative health care settings in Canada and throughout the world.

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The Canadian Society of Hospital Pharmacists assumes no responsibility for the statements and opinions advanced by contributors to the *Canadian Journal of Hospital Pharmacy*. Views expressed in the editorials are those of the authors and do not necessarily represent the official position of the Canadian Society of Hospital Pharmacists.

Mission du JCPH

Le JCPH est une revue spécialisée qui traite principalement des moyens que prennent les pharmaciens pour optimiser l'utilisation sûre et efficace des médicaments dans les hôpitaux et les autres milieux de soins de santé misant sur la collaboration au Canada et ailleurs dans le monde.

Vision du JCPH

L'objectif du JCPH est d'être une publication internationale respectée qui sert de plateau principal pour la dissémination de l'information en lien avec une pratique pharmaceutique axée sur le patient dans les hôpitaux et les autres milieux de soins de santé misant sur la collaboration au Canada et ailleurs dans le monde.

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La Société canadienne des pharmaciens d'hôpitaux n'est pas responsable des déclarations et des opinions émises par les collaborateurs au *Journal canadien de la pharmacie hospitalière*. Les points de vue exprimés dans les éditoriaux sont ceux de leurs auteurs et ne représentent pas nécessairement la position officielle de la Société canadienne des pharmaciens d'hôpitaux.

For Society enquiries / Pour les questions concernant la Société
Jody Ciufo
Chief Executive Officer / Directrice générale
ext. / poste 225
e-mail: jciufo@cshp.ca

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ADVERTISING/PUBLICITÉ
Canadian Society of Hospital Pharmacists
Manager, Marketing and Communications / Gestionnaire du marketing et des communications
ext. / poste 235
e-mail: advertising@cshp.ca

PRODUCTION
Janette Thompson, Jansom
Tel: 905.689.1058
Cell: 905.317.6788
e-mail: jansom@cogeco.ca

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EDITORIAL / ÉDITORIAL

ORIGINAL RESEARCH / RECHERCHE ORIGINALE

RESEARCH LETTER / COMMUNIQUÉ DE RECHERCHE

CASE REPORT / OBSERVATION CLINIQUE

POINT COUNTERPOINT / LE POUR ET LE CONTRE

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

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All correspondence concerning *CJHP* content and submissions to the Journal should be sent to the CSHP's offices in Ottawa. Contact information appears in the masthead. Submissions to the Journal can be made by logging in to *CJHP*'s Web-based system at http://cjhp.msubmit.net. Please note that we cannot accept articles submitted by facsimile or e-mail transmission.

New Horizons for the *Canadian Journal of Hospital Pharmacy*

Stephen Shalansky

The Canadian Society of Hospital Pharmacists (CSHP) is undergoing numerous changes, due in part to the impact of the COVID-19 pandemic on its financial situation. The *Canadian Journal of Hospital Pharmacy* (*CJHP*) is among the CSHP initiatives that will be joining this journey toward a more sustainable future. The recent events that prompted this re-evaluation have also presented an opportunity to rethink our approach to publishing the *CJHP*, which has remained largely unchanged for many years. After reviewing the latest readership data, the Editorial Board has carefully considered both the Journal's strengths and its areas for potential improvement, and how we might capitalize on the changing publication landscape. The aim is to improve all aspects of the way we publish the Journal, a resource that we have all trusted and relied upon over the years.

First, we are making some technological upgrades. For the purpose of manuscript submissions, we will be transitioning away from the current eJournalPress platform to Open Journal Systems (OJS) 3 software. In addition, we will be upgrading to the OJS 3 software system for Journal publication. OJS 3 offers a streamlined, fresh display and functional user interface. It provides a more straightforward submission process and includes a responsive design that adjusts to readers' screen size on smartphones and tablets, as well as on desktop computers. It will also streamline overall workflow for Journal staff. You will notice as well that the *CJHP* layout has been redesigned to an easier-to-read format.

CJHP will be reducing the number of issues published each year from six to four. This reduction in frequency will result in a slightly higher threshold for sending manuscripts out for review and for final acceptance. Another strategy for retaining quality while reducing the number of manuscripts published annually will be to omit some categories and update our Author Guidelines accordingly. As a result, the *CJHP* will no longer be publishing the following types of articles: stability studies, correspondence (including Research Letters), book reviews, and some types of editorials. We will also be ceasing the Advanced Pharmacist Practitioner series. At the same time, we will be introducing a new research category to accommodate shorter research reports (1500-word limit). The new category is being created in response to commonly encountered submissions that do not meet the requirements for a full-length Original Research manuscript, but include valuable information beyond the capacity of our traditional Research Letter criteria. We anticipate that many hospital pharmacy residency projects will be a good fit within this new category.

For the manuscript categories retained, we will be changing the word limits. For example, the abstract of Original Research articles will be limited to 250 words and the body of the article to 3000 words. The number and size of tables, figures, and references will also be re-evaluated and reduced where appropriate. We will also be implementing a 1500-word limit for the Innovations in Pharmacy Practice section and a 4000-word limit for Review articles. The Journal is also evaluating the possibility of a nominal submission fee (e.g., $100) for manuscripts accepted for publication, to help improve authors' commitment to quality before submission. The *CJHP's* Author Guidelines have been updated to include full details of these changes and are now available at https://www.cjhp-online.ca/public/author_guidelines_english.pdf

Finally, the *CJHP* is taking this opportunity to revamp our reviewer database. The quality of manuscripts accepted and published in the *CJHP* heavily relies on the input provided by our highly valued network of expert reviewers. We will be reaching out to existing reviewers to verify their continued interest, accurate contact information, and areas of expertise. We also encourage *CJHP* contributors and readers to volunteer as new reviewers and/or to suggest others. This will be a key step in maintaining and improving the quality of our Journal.

Change is not easy, but it is often required to flourish in a shifting landscape. Full implementation of these changes will take time and will require all of us to adjust our usual approach to submitting manuscripts as well as our expectations around the publishing process. There will likely be a lag as we process the healthy number of manuscripts already submitted and/or approved for publication. Our small publications team and volunteer Editorial Board have much work to do to accommodate these changes. Although

we will try to maintain similar turnaround times, some patience may be required on the part of those who submit manuscripts over the next few months. However, after everyone has adjusted to this new approach, we are confident that the result will be a higher-quality, more resilient version of the *Canadian Journal of Hospital Pharmacy*. We sincerely appreciate your support as we work through these processes, and we value your feedback along the way.

Stephen Shalansky, BSc(Pharm), PharmD, ACPR, FCSHP, is the Clinical Coordinator of the Pharmacy Department, Providence Health Care, and is a Clinical Professor in the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia. He is also the Editor of the *Canadian Journal of Hospital Pharmacy*.

Competing interests: None declared.

Address correspondence to:
Dr Stephen Shalansky
Pharmacy Department
Providence Health Care
1081 Burrard Street
Vancouver BC V6Z 1Y6

e-mail: sshalansky@providencehealth.bc.ca

ON THE FRONT COVER

Peggy's Cove, Nova Scotia

The cover photo was taken by Heather Foley when she was a student at the University of Waterloo, while attending the 2009 Canadian Pharmacists Association conference, where she was honoured as the recipient of the Centennial Leadership Award. Heather is now an Adjunct Clinical Assistant Professor in the University of Waterloo's School of Pharmacy. She is also the Regional Clinical Coordinator for the Windsor Area and works as a full-time pharmacist consulting for a nonprofit organization that provides patient care services.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.

De nouveaux horizons pour le *Journal canadien de la pharmacie hospitalière*

par Stephen Shalansky

La Société canadienne des pharmaciens d'hôpitaux (SCPH) subit actuellement de nombreux changements, en partie à cause des effets de la pandémie de COVID-19 sur sa situation financière. Le *Journal canadien de la pharmacie hospitalière* (JCPH) fait partie des initiatives de la SCPH qui visent à atteindre un avenir plus viable. Les récents événements ayant motivé cette réévaluation nous ont également permis de repenser notre approche concernant la publication du JCPH, qui est largement restée inchangée depuis de nombreuses années. Après avoir examiné les dernières données concernant le lectorat, le comité de rédaction a soigneusement examiné les forces et les domaines d'amélioration possibles du Journal ainsi que la manière de tirer profit de l'évolution du paysage de la publication. L'objectif vise à améliorer toutes nos façons de publier le Journal, qui est une ressource de confiance sur laquelle nous nous appuyons depuis de nombreuses années.

Nous y apportons tout d'abord des améliorations technologiques. En ce qui concerne la soumission des manuscrits, nous passerons de la plateforme actuelle (eJournalPress) au logiciel Open Journal Systems (OJS) 3. De plus, nous passerons au système OJS 3 pour la publication du Journal. Frais et épuré, l'affichage d'OJS 3 comprend également une interface d'utilisateur fonctionnelle. Elle facilite le processus de soumission, et sa conception dynamique s'adapte à la taille de l'écran des téléphones intelligents, des tablettes et des ordinateurs de bureau. La plateforme permettra en outre de simplifier le flux de travail du personnel du Journal. Vous remarquerez aussi que la présentation du JCPH a été remaniée et que ce format est maintenant plus facile à lire.

Le nombre annuel de numéros du JCPH sera lui aussi réduit et passera de six à quatre. Cette réduction de la fréquence de publication entraînera une légère élévation des critères pour l'envoi de manuscrits à réviser et pour l'acceptation finale. Une autre stratégie visant à préserver la qualité tout en réduisant le nombre de manuscrits publiés annuellement consistera à omettre certaines catégories et à actualiser nos directives en conséquence pour les auteurs. Par conséquent, les types d'articles suivants ne seront plus publiés dans le JCPH : études de stabilité, correspondance (y compris les Communiqués de recherche), critiques de livres ainsi que certains éditoriaux. Nous mettrons également fin à la série Pharmacien praticien avancé. Nous inaugurerons simultanément une nouvelle catégorie qui accueillera des rapports de recherche plus courts (limite de 1500 mots). Cette nouvelle catégorie vise à répondre aux soumissions fréquentes qui ne répondent pas aux exigences relatives à un manuscrit de recherche original de pleine longueur, mais qui comprennent de précieuses informations qui vont au-delà de nos critères relatifs aux Communiqués de recherche. Nous anticipons que de nombreux projets de résidence en pharmacie d'hôpital seront pertinents pour alimenter cette nouvelle catégorie.

Quant aux catégories de manuscrits retenues, nous modifierons la limite du nombre de mots. Par exemple, le résumé des articles des Recherche originales sera limité à 250 mots et le corps de l'article à 3000 mots. Le nombre et la taille des tableaux, leur volume de chiffres et des références seront eux aussi réévalués et réduits, le cas échéant. Nous imposerons aussi une limite de 1500 mots pour la section Innovations en pratique pharmaceutique ainsi qu'une limite de 4000 mots pour les articles Revues. Le Journal se penche également sur la possibilité d'imposer des frais de soumission nominaux (p. ex. 100 $) pour les manuscrits acceptés à des fins de publication, et cela afin d'améliorer l'engagement des auteurs à l'égard de la qualité de leurs écrits avant de les soumettre. Les directives pour les auteurs du JCPH ont été mises à jour et comprennent maintenant tous les détails de ces changements. Vous les trouverez à https://www.cjhp-online.ca/public/cjhp_directives_aux_auteurs.pdf

Enfin, le JCPH saisit cette opportunité pour remanier la base de données de ses examinateurs. La qualité des manuscrits acceptés et publiés dans le JCPH dépend fortement des commentaires émis par notre très précieux réseau d'experts. Nous contacterons nos examinateurs actuels pour nous assurer de leur intérêt, mais aussi pour vérifier leurs coordonnées et domaines d'expertise spécifiques. Nous encourageons également les contributeurs et les lecteurs du JCPH à se porter volontaires en tant que nouveaux examinateurs ou à en proposer d'autres. Ce sera ici une étape clé pour préserver et améliorer la qualité de notre journal.

Les changements ne sont pas simples, mais souvent nécessaires pour favoriser l'épanouissement du Journal dans un paysage en mutation. La mise en place complète de ces changements prendra du temps et nous demandera de modifier notre approche habituelle de la soumission des manuscrits ainsi que nos attentes concernant le processus de publication. Nous accuserons probablement un certain retard dans le traitement du nombre considérable de manuscrits déjà soumis ou approuvés pour leur publication. Notre petite équipe responsable des publications et notre comité éditorial ont fort à faire pour s'adapter à ces changements. Nous essaierons de maintenir des délais de traitement similaires à ceux auxquels sont habitués les auteurs, mais les personnes qui soumettent leur manuscrit devront toutefois s'armer de patience au cours des prochains mois. Cependant, une fois que chacun se sera adapté à cette nouvelle approche, nous sommes persuadés qu'il en résultera une version plus solide et de meilleure qualité du *Journal canadien de la pharmacie hospitalière*. Nous vous remercions sincèrement de votre soutien durant la mise en place de ces processus et nous accordons une grande importance aux commentaires que vous nous communiquerez à ce sujet.

[Traduction par l'éditeur]

Stephen Shalansky, B.Sc.(Pharm), Pharm.D., A.C.P.R., F.C.S.H.P., est coordinateur clinique du Département de pharmacie, Providence Health Care; il est aussi professeur clinique à la Faculté des sciences pharmaceutiques de l'Université de Colombie-Britannique à Vancouver, en Colombie-Britannique. Il est également rédacteur en chef du *Journal canadien de la pharmacie hospitalière*.

Conflits d'intérêts : Aucune déclaration.

Adresse de correspondance :
Dr Stephen Shalansky
Pharmacy Department
Providence Health Care
1081 Burrard Street
Vancouver BC V6Z 1Y6

Courriel : sshalansky@providencehealth.bc.ca

Providing Suitable Pediatric Formulations for Canadian Children: A Call for Action

Catherine Litalien, Julie Autmizguine, Antoine Carli, Denis Giroux, Denis Lebel, Jean-Marie Leclerc, Yves Théorêt, Andrea Gilpin, and Sophie Bérubé

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ABSTRACT

Background: Many medications given to children have no commercially available, age-appropriate formulations. This leads to manipulation of dosage forms designed for adults (compounding), which can result in an increased risk of dosing errors and adverse events, lack of medication adherence because of taste issues, and suboptimal dosing with therapeutic failure.

Objectives: To determine which drugs required compounding for oral administration to children in a Canadian hospital and, for each compounded drug, to determine whether it was available as licensed oral pediatric formulations in the United States or the European Union.

Methods: Drugs requiring compounded liquid formulations for oral administration, dispensed from January 1 to December 31, 2015, at a Canadian university-affiliated tertiary pediatric hospital, and prepared in a quantity exceeding 0.5 L per year, were retrospectively identified. The online drug databases of Health Canada, the US Food and Drug Administration, the European Medicines Agency (EMA), and the UK Medicines and Healthcare Products Regulatory Agency were searched to determine the availability of child-friendly oral formulations for these drugs. The regulatory status in each jurisdiction was also compared. For licensed formulations with potential concerns about excipient safety, EMA guidelines for sorbitol, propylene glycol, ethanol, and sodium benzoate were used to determine pediatric suitability.

Results: Of the 56 compounded drugs investigated, 27 (48%) had a suitable commercialized child-friendly formulation available outside Canada. Overall, these drugs had been on the Canadian market for a median of 35 years, and almost half (27 [48%]) had a pediatric indication in Canada.

Conclusions: Canada is lagging behind the United States and the European Union in ensuring availability of and access to suitable pediatric formulations. Potential explanations for this gap include small market size, regulatory uncertainties, and reimbursement shortcomings. Steps must be taken to implement pediatric-sensitive regulations and incentives, as well as reimbursement policies, to address these unmet needs.

Keywords: compounding, child-friendly medicines, pediatric oral medicines

RÉSUMÉ

Contexte : Plusieurs médicaments administrés aux enfants ne sont pas disponibles commercialement sous une forme pharmaceutique adaptée à leur âge. Ceci entraîne une manipulation des formes destinées aux adultes (préparation magistrale) et peut conduire à une augmentation du risque d'erreurs de dosage et d'effets indésirables, un manque d'observance médicamenteuse secondairement à des problèmes de goût, et un dosage sous-optimal associé à des échecs thérapeutiques.

Objectifs : Définir les médicaments qui exigent une préparation magistrale pour être administrés par voie orale aux enfants dans un hôpital canadien et, pour chaque médicament faisant l'objet d'une préparation magistrale, déterminer s'il est disponible sous une forme pharmaceutique orale autorisée pour les enfants aux États-Unis ou dans l'Union européene.

Méthodes : Les médicaments nécessitant des préparations magistrales liquides pour administration orale, distribués entre le 1er janvier et le 31 décembre 2015 dans un hôpital de soins pédiatriques tertiaires affilié à une université canadienne et dont la quantité préparée était supérieure à 0.5 L par an, ont été déterminés rétrospectivement. Les bases de données en ligne de médicaments de Santé Canada, de la Food and Drug Administration américaine, de l'Agence européenne des médicaments (AEM) et de la Medicines and Healthcare Products Regulatory Agency (Royaume-Uni) ont été interrogées pour déterminer la disponibilité de formes pharmaceutiques orales adaptées aux enfants pour ces médicaments. Le statut réglementaire de chaque pays a également fait l'objet d'une comparaison. Pour les formes pharmaceutiques autorisées présentant des problèmes potentiels d'innocuité des excipients, les directives de l'AEM concernant le sorbitol, le propylène glycol, l'éthanol et le benzoate de sodium ont servi à déterminer si un usage pédiatrique était acceptable.

Résultats : Des 56 médicaments étudiés faisant l'objet d'une préparation magistrale, 27 (48 %) avaient une forme pharmaceutique commercialisée adaptée aux enfants en dehors du Canada. Au total, ces médicaments sont sur le marché canadien depuis une médiane de 35 ans et près de la moitié (27 [48 %]) ont une indication pédiatrique au Canada.

Conclusions : Le Canada accuse un retard par rapport aux États-Unis et à l'Union européenne quant à la disponibilité et à l'accès à des formes pharmaceutiques adéquates pour les enfants. La petite taille du marché, les incertitudes en matière réglementaire et les lacunes concernant le remboursement pourraient notamment expliquer cet écart. Il est nécessaire de prendre des mesures pour mettre en place des réglementations et des incitatifs ainsi que des politiques de remboursement axés sur les enfants pour répondre à ces besoins criants.

Mots-clés : préparation magistrale, médicaments adaptés aux enfants, médicaments pédiatriques pour administration orale

INTRODUCTION

Every year, roughly half of Canada's 8 million children are given at least 1 prescription drug. The proportion is even higher among newborns and infants under the age of 1 year.[1] Despite their widespread use for children of all ages, from premature newborns to adolescents, many medications given to children have no commercially available, age-appropriate formulations. This situation leads to numerous challenges, including the need for health care professionals and caregivers to manipulate dosage forms designed for adults, a process referred to as compounding.[2,3] These manipulated medications fall outside of the Canadian regulatory approval process, and compounding results in "off-label" use of medications, with the efficacy and safety concerns that such use presents.[1] Lack of appropriate drug formulations for children can lead to increased risk of errors and adverse events, lack of adherence because of taste issues, and suboptimal dosing with therapeutic failure.[3-6] In addition, this practice uses time, money, and resources that could be directed to other aspects of pharmacy-related patient care if commercially available formulations were available.

Even though the practice of compounding is regulated by provincial pharmacy regulatory authorities and is essential to give young children access to medications, it should not be considered an equivalent surrogate for a pediatric formulation approved by Health Canada. Under the current requirements of Canada's Good Manufacturing Practices, compounded drugs are not overseen by Health Canada. Therefore, characteristics of compounded drugs are not as well established or controlled as those of approved formulations. This is particularly true with regard to stability, potency, content uniformity, purity, and bioavailability, among other characteristics.[2,7] Most importantly, administration of the appropriate dose cannot be guaranteed because of the variations outlined above.[8] Although every measure is taken to ensure that compounded drugs provide the most accurate dosing and are safe, errors do occur.[9,10] These errors can result in lack of efficacy or, at worst, major side effects; in extreme cases, death may occur, as for an 8-year-old Canadian boy who died in 2016 after the compounding pharmacy that dispensed his sleep medication (tryptophan) accidentally switched it for another medication (baclofen).[9]

To address these challenges and ensure safe and effective drug use in Canadian children, the Goodman Pediatric Formulations Centre (GPFC) was created in February 2016 to facilitate the development of and access to pharmaceutical-grade pediatric formulations.

As a first step toward this objective, the GPFC required a better understanding of the scope of the problem based on a patient-centric approach. The purpose of this study was to better define the unmet medical need for pediatric formulations in Canada by determining which drugs required compounding for oral administration in a Canadian tertiary pediatric hospital. For those compounded drugs, the availability and regulatory status of commercial pediatric oral formulations in the United States and/or the European Union were also determined.

METHODS

Data Collection

This retrospective study was conducted at the CHU Sainte-Justine, a Canadian university-affiliated tertiary pediatric hospital with 484 beds, in Montréal, Quebec. The hospital institutional review board deemed the study exempt from review.

The first step of the study was to identify drugs that required compounding for oral administration to children, which was accomplished using records in the CHU Sainte-Justine Pharmacy database. We included compounded oral liquid formulations dispensed from January 1 through December 31, 2015, and prepared in a quantity exceeding 0.5 L per year (a threshold chosen arbitrarily by the authors). Drugs for which splitting of an adult-formulation tablet was required were excluded because records for these drugs could not be retrieved from the Pharmacy database. Drugs compounded because of temporary back order during the study period were also excluded. The included drugs were subsequently classified according to the American Hospital Formulary Service Pharmacologic-Therapeutic Classification[11] according to their specific therapeutic uses.

The second step of the study was to determine whether the oral compounded drugs were available as licensed oral pediatric formulations in the United States and/or the European Union. These regions were chosen because they are the most advanced in terms of pediatric regulations, and drug information is easily accessible. For each drug, the online drug databases of Health Canada,[12] the US Food and Drug Administration (FDA),[13] and the European Medicines Agency (EMA)[14] were searched. For the European Union, if no commercialized pediatric formulations were identified in the EMA database, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) database[15] was searched. All databases were first searched on May 1, 2016. The Health Canada database was last accessed on February 28, 2019, whereas the other online databases were last accessed on September 30, 2018. From these website sources, product labels from all manufacturers were reviewed to extract the following data: the international nonproprietary name, the available dosage form(s), the strength (for capsules and tablets) or concentration (for oral liquid formulation) of the dosage form(s), the excipients, approved pediatric indications, and the approved lower age limit of the pediatric indication, if available. For Canada, the period since drug approval and patent status were also collected.

The medications were then classified into 4 categories on the basis of their commercial availability in the United States and/or the European Union, their pharmaceutical

form, and the excipients used, as described on the product label (Table 1).

As the third step of the study, a simulation was conducted for drugs in category 3 (those available as commercial liquid form containing excipients with potential safety concerns) to determine whether the excipients with potential safety concerns exceeded the maximum daily threshold described in recently published EMA guidelines. These are currently the only regulatory excipient guidelines with pediatric thresholds: for sorbitol, 140 mg/kg daily for all age groups[20]; for propylene glycol, 1 mg/kg daily for children up to 1 month of age, 50 mg/kg daily for children between 1 month and 5 years of age, and 500 mg/kg daily for children older than 5 years[21]; and for ethanol, 6 mg/kg daily for all age groups.[22] For sodium benzoate, the EMA guidelines are limited to neonates, for whom use of this excipient is prohibited[23]; as such, any drug containing this excipient was declared unsuitable for this age group. The simulation process was based on the concentration of the excipient(s) (either provided on the product label or obtained directly from the manufacturer), the concentration of the drug, the usual maximum daily dose (as determined by clinical practice and endorsed by hospital pharmacists at the study institution), and children's weight by age (as per World Health Organization growth charts).[24] When a liquid formulation was marketed by more than 1 manufacturer, the formulation with the lowest concentration of excipients was used for the simulation.

Quality Control

To ensure the quality and accuracy of the data, all data were extracted from the databases twice by different individuals (first extraction by 2 authors [A.C., D.G.] and 1 collaborator; second extraction by a third author [S.B.]). The authors discussed interpretation and classification issues during team meetings.

Statistical Analyses

Standard summary statistics, comprising percentages, medians, counts, and ranges to describe the study variables, were calculated using Excel for Mac, version 15.25.1 (160826) (Microsoft Corporation, Redmond, Washington). For the excipient exposure analysis, we first simulated a data set of children from birth to 12 years with weight distribution according to growth charts.[24] We created a subset of this data set consisting of 3 simulated children per month of age, with the 3rd, 50th, or 97th percentile of weight for age, using R software (n = 435).[25] For each oral formulation from category 3, we estimated the excipient exposure according to the following equation, using Excel and the Power Pivot add-in (Excel 2016, Microsoft Corporation):

$$\text{Excipient exposure (mg/day)} = \frac{\text{Weight (kg)} * \text{Dose (mg/kg/day)} * \text{Concentration}_{ex}\ \text{(mg/mL)}}{\text{Concentration}_{drug}\ \text{(mg/mL)}}$$

where Dose is the usual maximum daily dose (as determined in clinical practice and endorsed by hospital pharmacists at the study institution), $\text{Concentration}_{ex}$ is the concentration of the excipient in the oral formulation, and $\text{Concentration}_{drug}$ is the concentration of the drug in the oral formulation. The daily exposure (mg/day) was further divided by weight (kg). When the excipient component was expressed as V/V (volume of excipient/volume of liquid drug) in the monograph, we converted to milligrams per millilitre (i.e., weight/volume of liquid) by multiplying by the specific gravity of each excipient.[16]

RESULTS

A total of 86 drugs were compounded as liquid preparations for oral administration in the study hospital over the 1-year period. Thirty (35%) of these drugs were excluded, either because the quantity prepared annually was 0.5 L or less (n = 24), the quantity prepared could not be retrieved from the database (n = 1 [ketamine]), or the preparation was considered an outlier (n = 1 [unusually large quantity of glycine prepared for several family members being treated for a rare hereditary condition]). In addition, 1 drug was compounded because of a temporary back order (n = 1 [valganciclovir]), and 3 drugs were excluded because a pediatric

TABLE 1. Commercial Availability Categories

Category	Definitions	No. of Drugs (n = 56)
1	Available as commercial oral liquid with excipients known to be safe	14
2	Available as commercial nonliquid oral form, with ingredients known to be safe, such as chewable tablets and drugs requiring manipulation by the caregiver before administration (e.g., powder or granules for oral suspension/solution, scored tablets)	5
3	Available as commercial liquid form containing excipients with potential safety concerns, which could limit their use in pediatrics,[16,17] such as ethanol, sodium benzoate, propylene glycol, and/or sorbitol (according to recently published EMA guidelines on excipients[18,19])	12
4	No commercial pediatric formulation approved by FDA, EMA, or MHRA	25

EMA = European Medicines Agency, FDA = Food and Drug Administration (US), MHRA = Medicines and Healthcare Products Regulatory Agency (UK).

liquid formulation was approved and marketed in Canada (propranolol [Hemangiol], glycopyrrolate, and sevelamer) between the beginning and the end of the study.

As such, 56 drugs were included in the analysis, with annual volumes prepared ranging from 0.6 to 144 L (median 5.9 L/year). In most cases (50 [89%]), the compounded liquid formulations were prepared using approved tablets or capsules. Of the remaining 6 drugs, the commercially available IV formulation was used for oral administration of 2 medications (midazolam and vancomycin), and oral liquid solutions were prepared using a pharmaceutical grade powder as the active ingredient for 4 medications (arginine, caffeine, sodium benzoate, and sodium phosphate dibasic). One of the drugs (cisapride) was no longer on the Canadian market in 2015, but was available (and had been obtained) through the Special Access Programme of Health Canada.

The 3 most frequent therapeutic areas for compounded drugs were cardiovascular (n = 17 [30%]), central nervous system (n = 11 [20%]), and anti-infective drugs (n = 6 [11%]), and these accounted for 61% of all compounded liquid formulations. All 56 drugs were off-patent drugs and had been on the Canadian market for a median of 35 (range 14 to 65) years.

The distribution of the 56 drugs by category is shown in Table 1. Overall, 27 drugs (48%) requiring compounding for administration to children were found to have suitable commercially available, child-friendly formulations outside of Canada: 14 (25%) in category 1 (available as oral liquid with safe excipients; Table 2), 5 (9%) in category 2 (available as nonliquid oral form with safe excipients; Table 3), and 8 (14%) in category 3 (Table 4). The annual quantity of these 27 compounded drugs ranged from 0.6 to 144 L, with 9 (33%) of them prepared in quantities exceeding 25 L (Figure 1). Eighteen of these drugs had a pediatric indication in their Canadian product monograph.

For drugs with safe excipients available in the United States and the European Union as oral liquids (category 1)

TABLE 2. Oral Liquid Formulations with Excipients Known to Be Safe for Children and Available in the United States or Europe but not in Canada (Category 1, n = 14)

	Canada (Health Canada)		US (Food and Drug Administration)			Europe* (MHRA)		
Drug	Pediatric Indication†	Lower Age Limit	Pediatric Indication†	Lower Age Limit	Liquid Concentration, mg/mL (Form‡)	Pediatric Indication†	Lower Age Limit	Liquid Concentration, mg/mL (Form‡)
Amitriptyline§	Yes	12 years	Yes	12 years	None	Yes	6 years	10/25/50 (sol)
Amlodipine¶	Yes	6 years	Yes	6 years	None	Yes	6 years	1/2 (sol)
Enalapril	Yes	–	Yes	1 month	1 (sol)	Yes	–	None
Folic acid§**	Yes	1 year	Yes	–	None	Yes	From birth	1/2.5 (sol)
Levothyroxine	Yes	From birth	Yes	From birth	None	Yes	From birth	0.05/0.1/0.2 (sol)
Midazolam	Yes††	–	Yes	6 months	2 (syr)	Yes	3 months	5 (oms)‡‡
Nitrofurantoin	Yes	1 month	Yes	1 month	5 (susp)	Yes	3 months	5 (susp)
Phytonadione	Yes††	From birth	Yes††	From birth	None	Yes	From birth	10 (sol)§§
Rifampicin	Yes	–	Yes	–	None	Yes	1 month	20 (susp)
Captopril	No	18 years	No	18 years	None	Yes	from birth	1/5 (sol)
Gabapentin	No	18 years	Yes	3 years	50 (sol)	Yes	6 years	50 (sol)
Levetiracetam¶	No	18 years	Yes	1 month	100 (sol)	Yes	1 month	100 (sol)
Sotalol	No	18 years	Yes	–	5 (sol)	No	18 years	None
Caffeine¶**	No	18 years	Yes	From birth	10/20 (sol)	Yes	From birth	10/20 (sol)

Dash = not specified, "None" = liquid pediatric formulation unavailable.
*For all products, data were obtained from the UK Medicines and Healthcare Products Regulatory Agency (MHRA).
†For oral administration, unless specified otherwise.
‡Designations for pharmaceutical form: oms = oro-mucosal solution, sol = oral solution, susp = oral suspension, syr = syrup.
§At least one formulation available with safe excipients.
¶Amlodipine, levetiracetam, and caffeine oral solutions were not available in Canada at the time of study but have since been approved and commercialized in this country.
**Natural health product.
††Intravenous form only.
‡‡Prefilled syringes for oral use containing 0.5, 1, 1.5, or 2 mL.
§§Ampoules containing 2 mg in 0.2 mL, with oral dispensers provided in the pack.

or oral nonliquids (category 2), the pharmaceutical forms and their approved pediatric indication are compared with the Canadian label in Tables 2 and 3, respectively. Among the category 2 drugs, both topiramate and lamotrigine are currently available in Canada (as 15- and 25-mg capsules for sprinkling and as 2- and 5-mg chewable/dispersible tablets, respectively); compounding of these drugs into an oral liquid formulation was done mainly because of the lack of dosing flexibility with the current strengths available in Canada. The higher strengths available in the United States and the European Union offer more dosing flexibility for these 2 drugs.

Among 12 drugs available in commercial liquid forms containing excipients with potential safety concerns (category 3), 8 were found (by the simulation described above) to be suitable for use in children (Table 4). Based on the usual maximum daily dose, 2 drugs were found to be suitable for all ages, 5 were suitable for children older than 1 month, and 1 was considered suitable with the limitation that it may cause undesirable gastrointestinal effects secondary to excess amounts of sorbitol. Of these 8 drugs, 5 were found to have a pediatric indication in Canada. The remaining 4 medications in category 3 were classified as either unsuitable, because of the presence of ethanol above the recommended threshold, or unknown, because of insufficient data from the manufacturer to draw conclusions about suitability.

In addition to the 4 drugs from category 3 that were classified as unsuitable or inconclusive, 25 medications (45%) were found to have no commercialized pediatric oral formulations available in the United States or the European Union (EMA/MHRA) (category 4). The annual quantity of these compounded drugs ranged from 0.8 to 105 L, with 6 (21%) of them prepared in quantities of 25 L or more (Figure 2). Nine of these drugs had a pediatric indication in their Canadian product monographs.

DISCUSSION

This study represents the first step toward improving the availability of and access to age-appropriate drug formulations for Canadian children, because it provides pivotal information regarding the unmet need for pediatric formulations. We identified 56 drugs that were frequently compounded as oral liquid formulations and showed that for almost half of these drugs (48%), child-friendly oral formulations are commercially available in the United States and/or the European Union. It is difficult to explain why in a developed G7 country such as Canada, compounding of drugs that have been on the Canadian market for a median of 35 years is a standard of care for children, especially when these medications are available as suitable pediatric formulations elsewhere.

One striking example of how Canada is lagging behind other countries is the case of levetiracetam, a second-generation anti-epileptic drug that is widely used to manage partial seizures in children and adults.[26] In 2003, levetiracetam was approved in Canada for adults (18 years of age or older) with epilepsy, without mention of a pediatric indication or availability of a pediatric formulation.[27] It was only recently, in July 2019, that a pediatric indication was added to the Canadian product monograph, with approval of an oral solution, which is now (as of May 2020) commercialized in Canada. This situation contrasts with that in the United States and the European Union, where a pediatric indication for levetiracetam was granted in 2005, along with approval

TABLE 3. Oral Nonliquid Formulations with Excipients Known To Be Safe for Children and Available in the United States or Europe (Category 2, *n* = 5)

	Canada (Health Canada)			United States (Food and Drug Administration)			Europe* (EMA/MHRA)		
Drug	Pediatric Indication	Lower Age Limit (years)	Dosage Strength, mg (Form†)	Pediatric Indication	Lower Age Limit (years)	Dosage Strength, mg (Form†)	Pediatric Indication	Lower Age Limit (years)	Dosage Strength, mg (Form†)
Hydrocortisone	Yes	–	None	Yes	–	None	Yes	0	0.5/1/2/5 (gco)
Tacrolimus	Yes	–	None	Yes	–	0.2/1 (gs)	Yes	–	0.2/1 (gs)
Topiramate	Yes	2	15/25 (cs)‡	Yes	2	15/25 (cs)	Yes	2	15/25/50 (cs)
Lamotrigine	Yes	–	2/5 (cdt)‡	Yes	2	2/5/25 (cdt)	Yes	2	2/5/25/100 (cdt)
Hydroxyurea	no	18	None	Yes	2	100/1000 (st)	Yes	2	100/1000 (st)

Dash = not specified, EMA = European Medicines Agency, MHRA = UK Medicines and Healthcare Products Regulatory Agency, "None" = nonliquid pediatric formulation unavailable.

*Data for tacrolimus, topiramate, and lamotrigine were obtained from the MHRA; data for hydrocortisone and hydroxyurea were obtained from the EMA.

†Designations for pharmaceutical form: cdt = chewable dispersible tablet, cs = capsule to sprinkle, gco = granules in capsule for opening, gs = granules for suspension, st = scored tablet.

‡Despite the availability of pediatric-friendly dosage forms in Canada, the strengths available are not sufficient to cover pediatric dosage needs; therefore, these 2 formulations are considered suboptimal in Canada.

TABLE 4. Suitability of Oral Liquid Formulations with Potentially Harmful Excipients for Children Available in the United States or Europe (Category 3, *n* = 12)

Drug (Region*)	Potentially Harmful Excipient	Age Group for Which Toxic Threshold† Is Reached or Exceeded	Suitability for Children
Baclofen‡ 5 mg/5 mL (UK)	Propylene glycol	≤ 1 month Baclofen is not given to neonates; therefore, no simulation was done for this age group	**Suitable for children > 1 month of age** at a usual maximum dose of 20 mg/day for children > 1 month to 2 years of age or 40 mg/day for children > 2 years of age
Dexamethasone‡ 10 mg/5 mL 20 mg/5 mL (UK)	Sorbitol Propylene glycol	None ≤ 1 month	**Suitable for children > 1 month of age** at a usual maximum dose of 1 mg/kg daily
Domperidone§ 1 mg/mL (UK)	Sorbitol	All ages	May cause GI discomfort and mild laxative effects at usual maximum doses of 0.75 mg/kg daily for children ≤ 1 month of age and 2.4 mg/kg daily for children > 1 month old
Losartan‡ 2.5 mg/mL (EU)	Sorbitol	None	**Suitable for children of all ages** at usual maximum dose of 1.4 mg/kg daily
Metronidazole‡ 200 mg/5 mL (UK)	Sorbitol Propylene glycol	None ≤ 1 month	**Suitable for children > 1 month of age** at a usual maximum dose of 30 mg/kg daily
Sildenafil§¶ 10 mg/mL (EU)	Sorbitol	None	**Suitable for children of all ages** at the usual maximum dose of 4.0 mg/kg daily; may cause GI discomfort and mild laxative effects if used at doses > 5.6 mg/kg daily
Ursodiol§ 50 mg/mL (UK)	Propylene glycol Sodium benzoate	≤ 1 month No simulation conducted	**Suitable for children > 1 month of age** at a maximum dose of 30 mg/kg daily; product is contraindicated for neonates because of the presence of sodium benzoate, which may cause neonatal jaundice
Vancomycin‡ 25 and 50 mg/mL (US)	Sodium benzoate	No simulation conducted	**Suitable for children > 1 month of age;** product is contraindicated for neonates because it contains sodium benzoate, which may cause neonatal jaundice
Diazoxide‡ 50 mg/mL (US)	Ethanol	All ages	**Not suitable** for children at any age at a maximum dose of 10 mg/kg daily for children < 1 month of age, 15 mg/kg daily for children from 1 month to 1 year of age, and 8 mg/kg daily for children older than 1 year
Prednisone‡ 1 and 5 mg/mL (US)	Ethanol	All ages	**Not suitable** for children at any age at a maximum dose of 2 mg/kg daily
Levofloxacin§ 25 mg/mL (US)	Propylene glycol	No simulation conducted; amount of excipient not reported by the manufacturer	Unable to draw conclusions
Lorazepam§ 2 mg/mL (US)	Propylene glycol	No simulation conducted; amount of excipient not reported by the manufacturer	Unable to draw conclusions

EMA = European Medicines Agency, FDA = Food and Drug Administration (US), GI = gastrointestinal, MHRA = Medicines and Healthcare Products Regulatory Agency (UK).

*For designations of region, EU = drugs approved by the EMA, UK = drugs approved by the MHRA, and US = drugs approved by the FDA.

†Thresholds as per EMA guidance: for sorbitol, 140 mg/kg daily for all age groups[20]; for propylene glycol, 1 mg/kg daily for children up to 1 month of age, 50 mg/kg daily for children 1 month to 5 years of age, and 500 mg/kg daily for children older than 5 years[21]; for ethanol, 6 mg/kg daily for all age groups[22]; for sodium benzoate, the threshold is 0 for neonates (children under 1 month of age) only,[23] so any drug containing this excipient is declared unsuitable for this age group.

‡Solid oral dosage form approved for pediatric use in Canada.

§Solid oral dosage form not approved for pediatric use in Canada.

¶Powder reconstituted at the pharmacy.

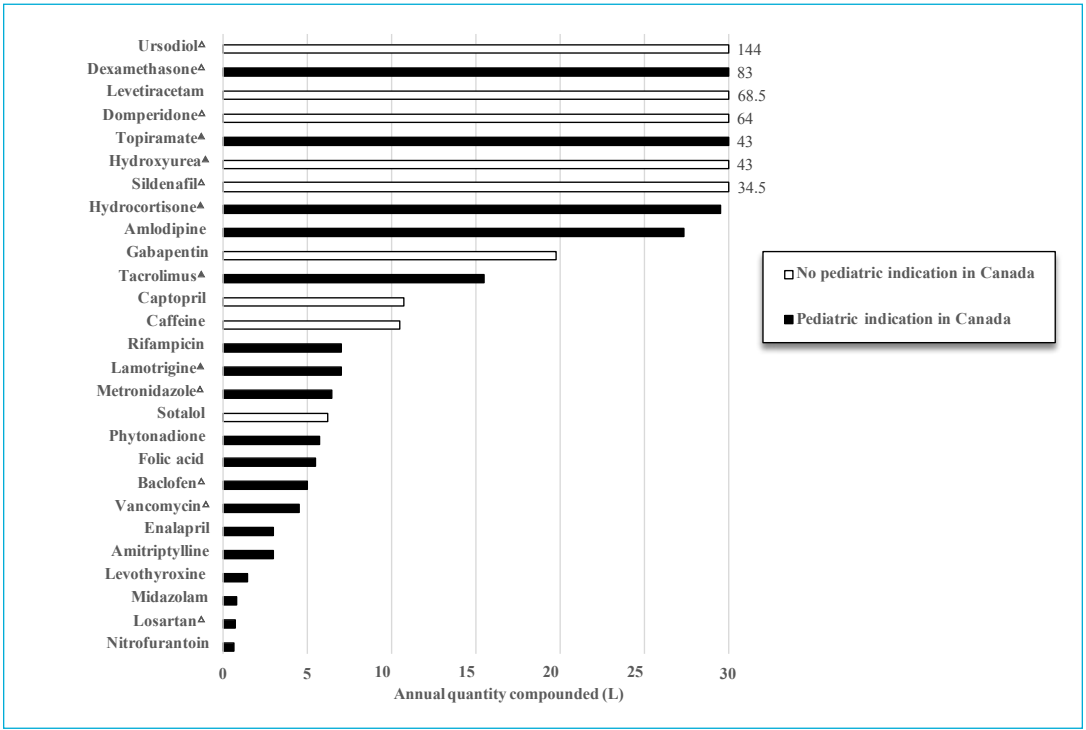

FIGURE 1. Annual quantity (L) and regulatory status of drugs compounded at a tertiary pediatric hospital for which commercial formulations suitable for children are available in the United States or the European Union (EMA/MHRA). Solid triangle = nonliquid oral form (category 2); open triangle = liquid oral form containing an excipient with potential safety concern (category 3). Levetiracetam and caffeine were not indicated for children at the time of database searching but are now indicated for pediatric use in Canada.

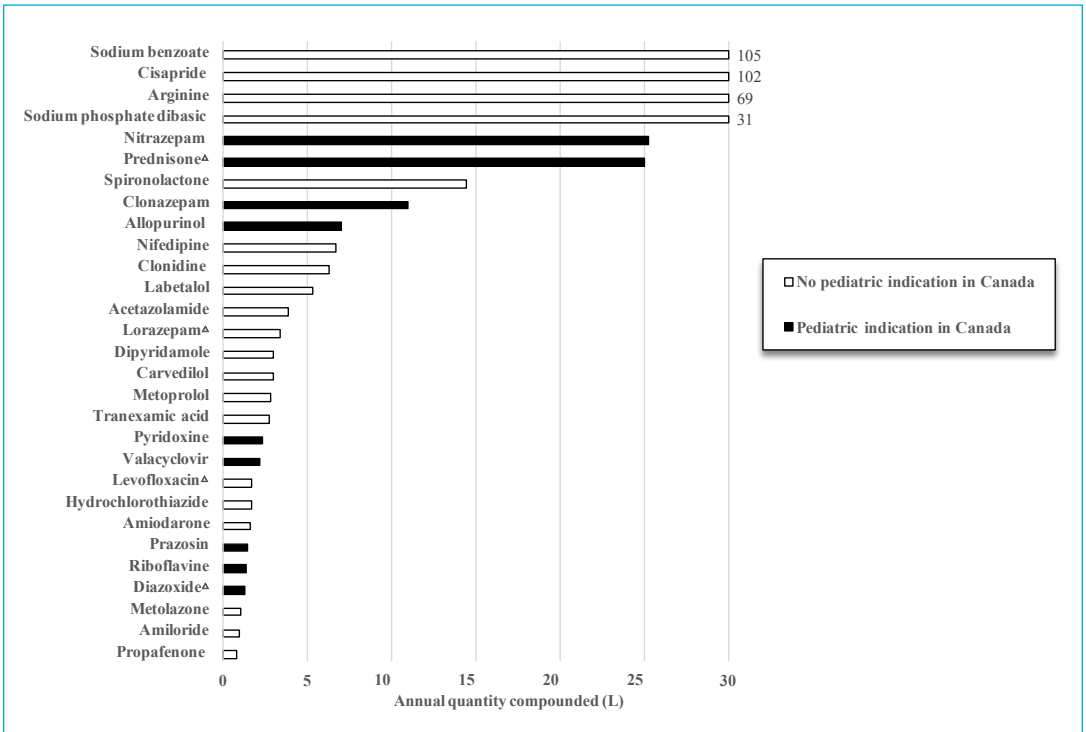

FIGURE 2. Annual quantity (L) and regulatory status of drugs compounded at a tertiary pediatric hospital for which no commercial formulation suitable for use in children is available in the United States or the European Union (EMA/MHRA). Open triangle = liquid oral form containing an excipient with potential safety concern (category 3).

of a child-friendly formulation.[28,29] This represents close to 15 years of delay for Canada, a situation that calls for action.

Our findings should prompt all stakeholders to ask why pediatric formulations are not being commercialized in Canada. We suspect that major reasons may include small market size (with Canada representing at most 2% of the global market),[30] along with regulatory uncertainties and reimbursement shortcomings. Compared with the United States and Europe, Canada falls behind in regulatory provisions related to pediatric drug development. Unlike Health Canada, the FDA and EMA have implemented specific regulations, through a system of requirements and incentives, to drive the development of appropriately licensed and formulated drugs for children, both patented and off-patent. With these systems in place, manufacturers are obliged to assess the safety and effectiveness of new drugs and biologics in pediatric patients if there is anticipated use in children, and incentives such as patent extensions may be provided to give manufacturers additional market exclusivity. These pediatric-specific regulations have translated into significant progress,[31] and Canada should build on these experiences.

Currently, Canada has no specific regulations for submission of pediatric formulations already approved in other countries. Recently, Health Canada has been evaluating a pathway for using foreign reviews and decisions to facilitate Canadian access to drugs, which was expected to come into effect in spring 2020,[32] but as of summer 2020 had not been endorsed. External consultations held in 2017 and 2018 indicated that this pathway will have reduced review timelines and fees, relative to the usual approval pathway. The 27 drugs identified in this study for which pediatric formulations are available in the United States and/or Europe would be ideal candidates to benefit from this initiative. However, we are concerned that the intent to require substantial international postmarket experience (i.e., 15 years) in other jurisdictions will constitute a major barrier, as it may disqualify many child-friendly medications.

Furthermore, under current policies, submissions for pediatric formulations do not meet the criteria for priority review. However, this situation may change in the near future, given Health Canada's release, at the end of May 2019, of the document *Draft Guidance: Accelerated Review of Human Drug Submissions*.[33] This accelerated review policy will encompass both the Priority Review of Drug Submissions policy and the Notice of Compliance with Conditions policy. It will thus provide an overarching policy by which critical drugs can be reviewed on an accelerated basis. The document specifically states that pediatric formulations could qualify for such accelerated review.

Once a drug is approved by Health Canada, significant barriers involving reimbursement and pricing may impede access to pediatric formulations. Depending on the medication type and its patent status, review by means of health technology assessment processes (through the Institut national d'excellence en santé et en services sociaux in Quebec and through the Canadian Agency for Drugs and Technologies in Health for the rest of Canada) may be needed. After the health technology assessment is complete, the drug must then be reviewed by the Patented Medicine Prices Review Board (if still on patent) and/or the Pan-Canadian Pharmaceutical Alliance (for both patented and generic medicines). Finally, the public drug plan in each province evaluates whether it will list, and therefore pay for, the new drug, on the basis of a budget comparison against the established cost of current treatment.[26] Many of these evaluation processes are built on criteria applicable to adult forms, which may not apply, or may not be possible, in children. Hence, reimbursement for a pediatric formulation may be rejected. A recent example of this unfortunate situation occurred with Hemangiol, a pediatric propranolol solution approved by Health Canada and reimbursed in over 20 countries for the treatment of infantile hemangioma. Neither of the Canadian health technology assessment agencies supported its reimbursement because they used, for purposes of their budget impact analysis, the cost of the compounded propranolol formulation (which is relatively inexpensive) and therefore evaluated Hemangiol as being too expensive. It is impossible for a medication that has been manufactured in a highly controlled environment in accordance with Good Manufacturing Practices, and for which pediatric studies (with their associated costs) have been performed, to be comparable in price to a compounded preparation of the same drug, especially when the drug of interest is old and inexpensive. After further negotiation between the parties involved, Hemangiol is now reimbursed and available to Canadian children (Islam Mahmoud, Pierre Fabre Laboratories; personal communication, July 15, 2020) but some challenges, which are beyond the scope of this article, still remain for health care providers and for patients and their families. This case reinforces the need for alignment between regulatory and reimbursement processes, as well as the need to develop pediatric-specific criteria for drug evaluation by health technology assessment bodies, with recognition of the added safety and efficacy of a commercial pediatric formulation over a compounded preparation.

To encourage commercialization of off-patent drugs for children, the EMA instituted, as part of the European Union's 2007 pediatric legislation, the Paediatric Use Market Authorisation program, which offers 10 years of data exclusivity for the development and commercialization of pediatric formulations of older drugs.[34] Ten years after implementation of the legislation, this program has not been as successful as anticipated. One potential explanation for this outcome is the lack of alignment between regulatory and reimbursement systems, given that reimbursement processes are country-specific.

We also identified 29 frequently compounded drugs for which no suitable pediatric formulation was marketed in the United States or the European Union (EMA/MHRA). A

classic example is clonidine, which has been on the Canadian market for over 40 years and is still used as an off-label compounded formulation for children of all ages, for multiple conditions such as hypertension, neonatal abstinence syndrome, agitation and pain in the pediatric intensive care unit, and attention deficit/hyperactivity disorder, to name just a few. To address this gap, the development of innovative dosage forms, such as mini-tablets, in addition to liquid forms, should be considered. We truly hope that in the near future, with all of the available technologies, international multidisciplinary collaborations involving regulators, reimbursement bodies, industry, and other major stakeholders will result in the successful development of pediatric formulations of old drugs.

Our study had some limitations. It focused on frequently compounded drugs in a university-affiliated tertiary pediatric hospital, which may not accurately reflect the compounding reality of community hospitals or the outpatient setting (although many of the included drugs are often used outside the hospital). Because only medications compounded as oral liquid formulations were studied, some commonly compounded medications that undergo tablet splitting were not included; as such, our results likely underestimate the need for pediatric formulations. Furthermore, this study does not provide information about compounding of drugs that are administered parenterally (i.e., by IV, intramuscular, topical, and other routes). We considered the regulatory status and availability of these compounded medications only in the United States and the European Union (with information on drug status and availability coming mainly from the MHRA database); thus, we may have missed suitable pediatric formulations marketed in other jurisdictions. Finally, because the approval of drugs is an ongoing process, the situation for some drugs may have changed between the time the databases were last accessed and the time of publication. This has already occurred for amlodipine, levetiracetam, and caffeine oral solutions, which were not available as pediatric formulations at the time of database searching but are now (summer 2020) approved and commercialized in Canada for pediatric use.

CONCLUSION

What emerges from this study is that Canada is clearly lagging behind the United States and Europe in ensuring availability of and access to suitable pediatric formulations in a timely manner. Children account for almost one-fifth of the Canadian population, and they deserve the same standards as adults in terms of pharmaceutical forms designed to suit their needs, so as to maximize drug efficacy and safety. Steps must be taken to implement pediatric-sensitive regulations and incentives, as well as reimbursement policies, to fill this important gap. Furthermore, collaboration among all stakeholders is urgently needed to better understand the obstacles and hurdles from everyone's perspective, with the ultimate goal of defining for Canada a new sustainable model that will address the unmet needs for pediatric formulations of old off-patent drugs, as well as new drugs.

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Catherine Litalien, MD, FRCPC, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre, the Department of Medical Biology, and the Research Centre of the CHU Sainte-Justine, Montréal, Quebec. She is also with the Department of Pediatrics and the Department of Pharmacology and Physiology, Université de Montréal, Montréal, Quebec.

Julie Autmizguine, MD, FRCPC, MSc, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre, the Department of Medical Biology, and the Research Centre of the CHU Sainte-Justine, Montréal, Quebec. She is also with the Department of Pediatrics and the Department of Pharmacology and Physiology, Université de Montréal, Montréal, Quebec.

Antoine Carli, BPharm, MSc, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre of the CHU Sainte-Justine, Montréal, Quebec.

Denis Giroux, BPharm, MSc, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre of the CHU Sainte-Justine, Montréal, Quebec.

Denis Lebel, BPharm, MSc, FCSHP, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre and the Department of Pharmacy, CHU Sainte-Justine, Montréal, Quebec.

Jean-Marie Leclerc, MD, FRCPC, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre and the Department of Medical Biology of the CHU Sainte-Justine, Montréal, Quebec. He is also with the Department of Pediatrics, Université de Montréal, Montréal, Quebec.

Yves Théorêt, BPharm, PhD, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre, the Department of Medical Biology, and the Research Centre of the CHU Sainte-Justine, Montréal, Quebec. He is also with the Department of Pharmacology and Physiology, Université de Montréal, Montréal, Quebec.

Andrea Gilpin, PhD, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre of the CHU Sainte-Justine, Montréal, Quebec.

Sophie Bérubé, BPharm, MSc, is with the Rosalind & Morris Goodman Family Pediatric Formulations Centre of the CHU Sainte-Justine, Montréal, Quebec.

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Address correspondence to:
Dr Catherine Litalien
CHU Sainte-Justine
3175, chemin de la Côte-Sainte-Catherine
Montréal QC H3T 1C5

e-mail: catherine.litalien.hsj@ssss.gouv.qc.ca

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Survey of Drug Information Database Preferences among Staff from Selected British Columbia Health Authorities

Yiu-Ching Jennifer Wong, Candy Lee, and Adil Virani

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ABSTRACT

Background: With the increasing use of electronic point-of-care resources, it is imperative to clearly understand what health professionals consider valuable when selecting a drug information database. A current analysis of the preferences of staff in selected British Columbia health authorities was deemed helpful for determining which electronic drug information database should be purchased.

Objectives: To determine the factors that BC hospital pharmacists, nurses, and other health professionals value in an electronic drug information database and to better understand the general preferences of staff in choosing between the Lexicomp and Micromedex databases.

Methods: An electronic survey was created for data collection. The survey was open from August 10 to September 15, 2018, and again from November 11 to December 7, 2018. The survey link was sent by e-mail to staff in the following health authorities: Fraser Health, Providence Health Care, Provincial Health Services Authority, and Vancouver Coastal Health. Qualitative and quantitative methods were used to analyze the survey data.

Results: A total of 247 responses were received, of which 145 (58.7%) were complete. Completed surveys were received from 77 pharmacists, 52 nurses, and 16 other health professionals. Participants ranked dosing information and ease of use as the most important factors that they considered when choosing a drug information database. There were no significant differences between the Lexicomp and Micromedex resources in terms of usability, quality, and preference.

Conclusions: This survey provided insights into what BC health authority staff perceive as important when utilizing a drug information database. Those considering either renewing or initiating a subscription to an online drug information database can use these results to better understand the preferences of health care professionals. Survey respondents ranked dosing information and ease of use as the 2 most important factors in selecting a drug information database. Pharmacists were more particular about using their preferred database than were other health professionals.

Keywords: drug information databases, pharmacists, nurses, health authority staff, preferences

RÉSUMÉ

Contexte : Avec l'utilisation croissante de ressources électroniques aux points de services, il est impératif de bien comprendre ce que les professionnels de la santé estiment important lorsqu'ils choisissent une base de données sur les médicaments. Une analyse actuelle des préférences des membres du personnel des autorités sanitaires sélectionnées de la Colombie-Britannique a été jugée utile pour déterminer le type de base de données sur les médicaments à acheter.

Objectifs : Déterminer quels facteurs sont importants pour les pharmaciens d'hôpitaux, les infirmiers et les autres professionnels de la santé de la C.-B. lors du choix d'une base de données électronique sur les médicaments et mieux cerner les préférences générales des membres du personnel lorsqu'ils choisissent entre les bases de données Lexicomp et Micromedex.

Méthodes : Un sondage électronique a servi à la collecte des données. Il s'est déroulé du 10 août au 15 septembre 2018, et à nouveau du 11 novembre au 7 décembre 2018. Les membres du personnel des autorités sanitaires suivantes ont reçu le lien menant au sondage : Fraser Health, Providence Health Care, Provincial Health Services Authority et Vancouver Coastal Health. L'analyse des données a été effectuée à l'aide de méthodes qualitatives et quantitatives.

Résultats : Les investigateurs ont reçu 247 réponses, dont 145 étaient complètes (58,7 %). Soixante-dix-sept (77) pharmaciens, 52 infirmiers et 16 autres professionnels de la santé ont dument rempli le sondage. Les participants ont indiqué que les renseignements sur le dosage et la facilité d'utilisation étaient les deux facteurs les plus importants à prendre en compte lors du choix d'une base de données sur les médicaments. Aucune différence significative n'est ressortie entre les bases de données Lexicomp et Micromedex quant à l'opérabilité, la qualité et la préférence.

Conclusions : Ce sondage a permis de fournir un aperçu sur ce que les membres du personnel des autorités sanitaires de la C.-B. percevaient comme important pour l'utilisation d'une base de données sur les médicaments. Les personnes qui ont l'intention de renouveler ou de souscrire un abonnement à une base de données sur les médicaments en ligne peuvent utiliser ces résultats pour mieux cerner les préférences des professionnels de la santé. Les répondants ont indiqué que les renseignements sur le dosage et la facilité d'utilisation étaient les deux facteurs les plus importants à prendre en compte lors du choix d'une base de données sur les médicaments. Les pharmaciens étaient moins disposés que les autres professionnels de la santé à changer leur base de données préférée pour une autre.

Mots-clés : base de données sur les médicaments, pharmaciens, infirmiers, membres du personnel des autorités sanitaires, préférences

INTRODUCTION

As the volume of drug information expands, it becomes essential for health professionals to have a comprehensive, accurate, and efficient drug information resource readily available. The rapid advancement of technology enables health professionals to shift from physical reference books to electronic drug information databases, either in web-based or app-based format. Online drug information databases are accessible for free or through subscriptions. Despite the numerous databases available, most health authorities in British Columbia have limited resources and purchase a single electronic drug information database subscription at a time. Therefore, it is in the health authorities' interest to subscribe to the most well-rounded and cost-effective online database.

Subscription decisions should be based on the perceptions and preferences of health professionals (i.e., the users) regarding the quality, performance, usability, and value of the drug information databases that are available. A study conducted in 2010 compared BC hospital pharmacists' preferences concerning several drug information databases according to their usability and quality.[1] To the best of our knowledge, there have been no studies investigating other Canadian health professionals' opinions. Given that online resources develop rapidly, a more up-to-date analysis is needed to understand what BC health authorities' staff members consider most important when choosing an online drug information database.

Lexicomp (Wolters Kluwer) and Micromedex (IBM Corporation) are the 2 electronic drug information databases to which BC health authorities currently subscribe most often. Since 2012, the Fraser Health Authority, Providence Health Care, the Provincial Health Services Authority, and Vancouver Coastal Health in the Lower Mainland have subscribed to both the web-based and the app-based versions of Lexicomp, with the web-based version being available on desktop computers through each health authority's intranet. Hospital staff can also download the app-based version to their personal or work cellphones. Of these 4 health authorities, only the Provincial Health Services Authority has active subscriptions to both Lexicomp and Micromedex (web-based version for both). The proportion of staff members in this health authority using Lexicomp or Micromedex as their main online drug resource varies by site. Notably, the Micromedex app is not part of the Provincial Health Services Authority's subscription. In fact, this app was free to the public during our study period. The web-based Micromedex database was recently revamped to incorporate features such as "ask Watson" and Canadian-specific drug information. To test the revised version, the publisher of Micromedex offered all of the health authorities in the Lower Mainland temporary access to the web-based database from August 2 to December 7, 2018. With the database subscriptions of several health authorities up for renewal, the availability of trial access to the web-based version of Micromedex, concurrent with ongoing access to Lexicomp, presented a good opportunity to conduct a program evaluation study and to investigate staff preferences between the 2 online drug resources.

For this quantitative and qualitative program evaluation analysis, we created a survey to investigate the main factors that staff members of Fraser Health, Providence Health Care, the Provincial Health Services Authority, and Vancouver Coastal Health take into consideration when choosing a web-based drug information database. In addition, we investigated staff members' general preference between Lexicomp and Micromedex (web-based versions) as their primary drug information database.

METHODS

A prospective, cross-sectional survey was created online via Qualtrics software (see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/201/showToc). The online survey was initially available to potential participants between August 10 and September 15, 2018. This period yielded a low number of completed responses, so the survey was reopened from November 11 to December 7, 2018. The survey was exempted from Fraser Health ethics review because it was considered a program evaluation study.

A convenience sampling method was used. Information about this program evaluation and a link to the anonymous survey were distributed by e-mail to the 480 pharmacists employed at the time by Lower Mainland Pharmacy Services, with weekly reminder e-mails. Survey information and the link were also sent by e-mail to directors and managers of other health professionals within the 4 health authorities for further distribution to physicians and nurses, with weekly reminder e-mails. Only individuals who completed the survey were included in the analysis. All participants were asked to sign a consent form on page 1 of the electronic questionnaire. A link to the revised web-based version of Micromedex was embedded in the survey for participants who were new to the database, to allow experimentation before completing the survey.

The survey consisted of 14 questions (see Appendix 1). Partial responses were saved for up to 24 h, allowing participants to return to where they left off. Participants had to complete each question before proceeding to the next one.

Content of Survey

Collection of demographic information: Participants were asked about their profession, number of years practising in a hospital setting, primary role in practice, prior experience with the Lexicomp and Micromedex databases, and frequency and purpose of using the drug information databases.

Evaluation of factors deemed important to participants: Participants were asked to choose the top 3 factors influencing their choice of a preferred drug information database. A list of factors based on a previous publication[2] was presented to participants. Distribution of the favoured factors was stratified by profession.

Evaluation of database usability: Participants were asked to complete a usability questionnaire for the Lexicomp and/or Micromedex database. The usability questionnaire was adapted from previous publications.[3,4] For each of 7 usability domains for each database (database layout, navigation, speed, accuracy of content, amount of information, capability to solve drug-related questions, and user satisfaction), the answer options were presented as a 5-point Likert scale, ranging from "strongly disagree" to "strongly agree". A mean score was calculated for each domain within each database.

Evaluation of overall quality and preference: Participants' thoughts about the overall quality of the 2 databases were determined by asking participants to choose either Lexicomp or Micromedex as the drug information database they considered as having better quality. Participants were similarly asked about their overall preference between the 2 drug information databases. The distribution of preference was stratified by profession.

Evaluation of willingness to switch from a preferred database: Participants' willingness to switch from a preferred database was assessed by cost. More specifically, participants were asked to choose the relative price reduction (as a percentage [10%, 30%, 50%, 70%] or no preference) that would justify the cost-effectiveness of switching to a less preferred database.[5]

Statistical Analysis

Data regarding differences in usability score between the Lexicomp and Micromedex databases were analyzed quantitatively with descriptive (mean scores with 95% confidence intervals) and inferential (unpaired 2-sample *t* tests) statistics. The statistical analyses were performed with Excel software (Microsoft Corporation). Values of p below 0.05 were considered statistically significant.

Qualitative Analysis

Bar graphs were used to illustrate the distribution of participants' overall database preferences, the databases' overall quality, and participants' willingness to switch from their preferred database.

RESULTS

Of the 247 responses received, 145 (58.7%) were complete. Most of the participants were pharmacists (77 [53.1%]) and nurses (52 [35.9%]). The other health professionals included nurse practitioners and physicians, among others (16 [11.0%]) (Figure 1).

Instead of sending the survey information and link through the survey software (Qualtrics), we relied on pharmacy leaders to distribute the survey invitation to all relevant health professionals. Therefore, the total number of health professionals (other than pharmacists) who received the e-mail with the survey link was unknown. We were also unable to determine the number of e-mail messages that were received, opened, or read. As a result, the response rate in relation to the number of health professionals in the 4 health authorities could not be accurately calculated. The 77 pharmacists who completed the survey represented 16.0% of the 480 hospital pharmacists to whom the survey link was sent, assuming that all e-mail addresses in the Lower Mainland distribution list for pharmacists were active. Nonetheless, when we examined the demographic data in Table 1, particularly years of practice and primary roles in practice, we found that participants in this survey accurately represented health professionals in British Columbia.[6]

Characteristics of Participants

Most participants (92 [63.4%]) had been practising for more than 10 years, and most (102 [70.3%]) worked in a direct patient care setting (Table 1). Most of the pharmacists reported using a drug information database a few times a day to search for drug dosages, drug interactions, and adverse drug reactions (Table 2). The other health professionals mostly reported using a drug information database weekly for similar reasons (Table 2).

Factors Deemed Important to Participants

When deciding on a drug information database, factors such as dosing information, ease of use, and drug interaction information had the strongest influence on pharmacists' decisions. Nurses considered factors such as dosing information, ease of use, and IV compatibilities as being most important. In addition to dosing information and ease of use, the other health professionals thought that information about approved indications was a crucial element (Table 3).

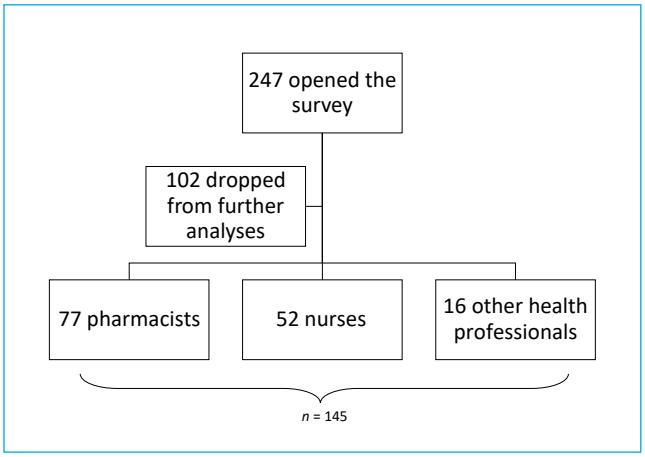

FIGURE 1. Flow chart for responses to the survey.

TABLE 1. Characteristics of Participants

Characteristic	Health Profession; No. (%) of Respondents*					
	Pharmacists (*n* = 77)		Nurses (*n* = 52)		Others (*n* = 16)	
Completed responses (*n* = 145)	77	(53.1)	52	(35.9)	16	(11.0)
Years of practice						
< 5 years	14	(18)	6	(12)	6	(38)
5–10 years	11	(14)	13	(25)	3	(19)
> 10 years	52	(68)	33	(63)	7	(44)
Primary role in practice						
Clinical (direct patient care)	57	(74)	33	(63)	12	(75)
Dispensary	9	(12)	NA		NA	
Others	11	(14)	19	(37)	4	(25)
Prior access to drug information databases						
Lexicomp only	15	(19)	36	(69)	9	(56)
Micromedex only	2	(3)	5	(10)	1	(<1)
Both	60	(78)	11	(21)	6	(38)
Frequency of using databases						
Few times a day	65	(84)	12	(23)	9	(56)
Once daily	7	(9)	9	(17)	0	(0)
Every other day	1	(1)	6	(12)	2	(12)
Weekly	4	(5)	17	(33)	2	(12)
Every other week	0	(0)	4	(8)	0	(0)
Less than once a month	0	(0)	4	(8)	3	(19)

NA = not applicable.
*For the first row, the denominator for calculating percentages was 145 (the number of complete survey responses). For all subsequent rows, the denominators were the *n* values at the top of each column (the number of complete survey responses in each category of health professionals).

TABLE 2. Purposes for Use of Drug Information Databases

Purpose†	Health Profession; No. (%) of Respondents*					
	Pharmacists (*n* = 77)		Nurses (*n* = 52)		Others (*n* = 16)	
Adverse drug reactions	71	(92)	35	(67)	13	(81)
Approved indications	40	(52)	22	(42)	9	(56)
Contraindications	41	(53)	32	(62)	13	(81)
Drug dosages	70	(91)	35	(67)	15	(94)
Drug identification	12	(16)	18	(35)	2	(12)
Drug interactions	71	(92)	30	(58)	14	(88)
IV compatibilities	32	(42)	41	(79)	2	(12)
Patient counselling information	29	(38)	18	(35)	8	(50)
Pharmacokinetic parameters	58	(75)	6	(12)	5	(31)
Pregnancy and lactation	29	(38)	7	(13)	4	(25)
Toxicology	17	(22)	8	(15)	0	(0)
Others	5	(6)	3	(6)	2	(12)

*For all rows, the denominators were the *n* values at the top of each column (the number of complete survey responses in each category of health professionals).
†Respondents could select as many responses as were appropriate to their practice.

TABLE 3. Factors Deemed Important by Health Professionals

Factor*	Health Profession; No. (%) of Respondents†							
	Pharmacists (*n* = 77)		Nurses (*n* = 52)		Others (*n* = 16)		All (*n* = 145)	
Dosing information	41	(53)	17	(33)	8	(50)	66	(46)
Ease of use	32	(42)	26	(50)	10	(62)	68	(47)
Drug interaction information	30	(39)	8	(15)	3	(19)	41	(28)
Canadian-specific drug information	20	(26)	13	(25)	2	(12)	35	(24)
Pharmacokinetic information	19	(25)	2	(4)	0	(0)	21	(14)
Adverse drug events	19	(25)	8	(15)	3	(19)	30	(21)
Availability of app version	14	(18)	6	(12)	2	(12)	22	(15)
Comparative efficacy of drugs	10	(13)	1	(2)	0	(0)	11	(8)
Patient management/monitoring parameters	8	(10)	10	(19)	3	(19)	21	(14)
Screen layout	6	(8)	5	(10)	2	(12)	13	(9)
Side effects	6	(8)	10	(19)	2	(12)	18	(12)
IV compatibilities	6	(8)	19	(37)	0	(0)	25	(17)
Approved indications	5	(6)	4	(8)	4	(25)	13	(9)
Speed	4	(5)	8	(15)	1	(6)	13	(9)
Cost	2	(3)	0	(0)	2	(12)	4	(3)
Precautions and contraindications	2	(3)	7	(13)	2	(12)	11	(8)
Drug identification information	1	(1)	5	(10)	0	(0)	6	(4)
Pregnancy and breastfeeding information	0	(0)	2	(4)	0	(0)	2	(1)
Patient counselling information	0	(0)	4	(8)	0	(0)	4	(3)
Toxicology	0	(0)	0	(0)	0	(0)	0	(0)
Other	6	(8)	1	(2)	2	(12)	9	(6)

*Factors are ordered from most to least important in terms of pharmacists' responses (with "other" presented last).
†Each participant was asked to choose the top 3 from a predefined list of factors; therefore, the percentages do not sum to 100%.

Database Usability

In the side-by-side comparison of the Lexicomp and Micromedex databases across 7 usability domains, Lexicomp was rated higher on screen layout, ease of use, speed, and accuracy, whereas Micromedex was rated higher on sufficiency of information provided, capability to solve drug-related questions, and performance to satisfy participants' needs (Table 4). However, the differences between the databases in terms of these ratings were not statistically significant.

Overall Quality

The largest proportion of pharmacists (*n* = 33) ranked Micromedex as the drug information database with better overall quality. The largest proportions of nurses (*n* = 20) and other health professionals (*n* = 8) had no preference (Figure 2). Of the 22 nurses who had a preference, most chose Micromedex (*n* = 13).

Overall Preference

In terms of overall preference, more pharmacists preferred Lexicomp than preferred Micromedex (35 versus 32). Once again, many of the nurses (*n* = 15) and other health professionals (*n* = 5) had no preference (Figure 3). Of the 26 nurses who expressed a preference, more picked Micromedex than Lexicomp (14 versus 12).

Preferences in the Context of Database Cost

Participants were asked to choose the relative price reduction (as a percentage) that would be needed for them to switch to a less preferred database. The largest proportion of pharmacists (*n* = 21) stated that a 70% cost reduction would be needed to persuade them to switch (Figure 4). Among nursing and other health professionals, the largest proportion had no preference between the 2 databases.

TABLE 4. Usability Scores for Micromedex and Lexicomp Databases

Quality Indicator	Database; Mean Usability Score (95% CI)*			
	Micromedex		Lexicomp	
Layout of the screens was clear	3.91	(3.72–4.10)	4.09	(3.95–4.23)
Navigating within this database was easy	3.88	(3.67–4.09)	4.07	(3.92–4.22)
Speed of this database was fast	4.14	(3.97–4.31)	4.19	(4.07–4.31)
The content in this database was accurate	4.02	(3.85–4.19)	4.09	(3.97–4.21)
The amount of information provided from this database was sufficient	4.11	(3.92–4.30)	3.72	(3.56–3.88)
This database was able to solve my drug-related questions	4.04	(3.86–4.22)	3.82	(3.66–3.98)
Overall, the performance of this database was able to satisfy my needs	3.98	(3.77–4.19)	3.91	(3.75–4.07)

CI = confidence interval.
*The usability score was rated from 1 (strongly disagree) to 5 (strongly agree) on a Likert-type scale.

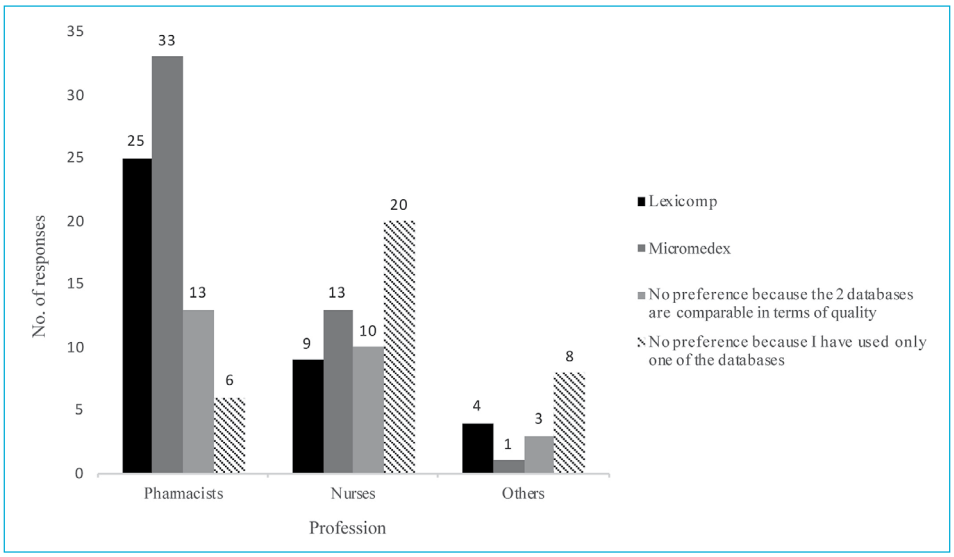

FIGURE 2. Distribution of databases deemed to have better quality, by profession (n = 145).

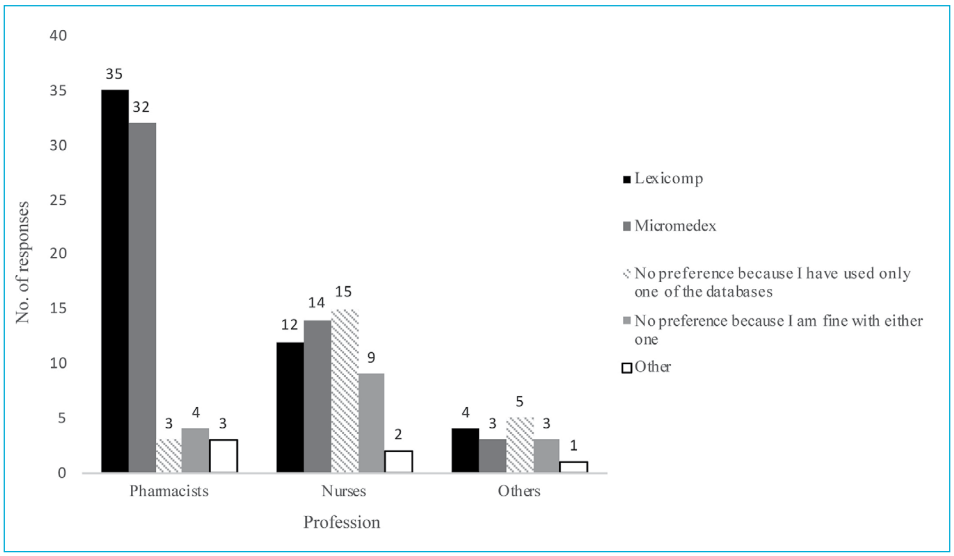

FIGURE 3. Distribution of overall database preferences, by profession (n = 145).

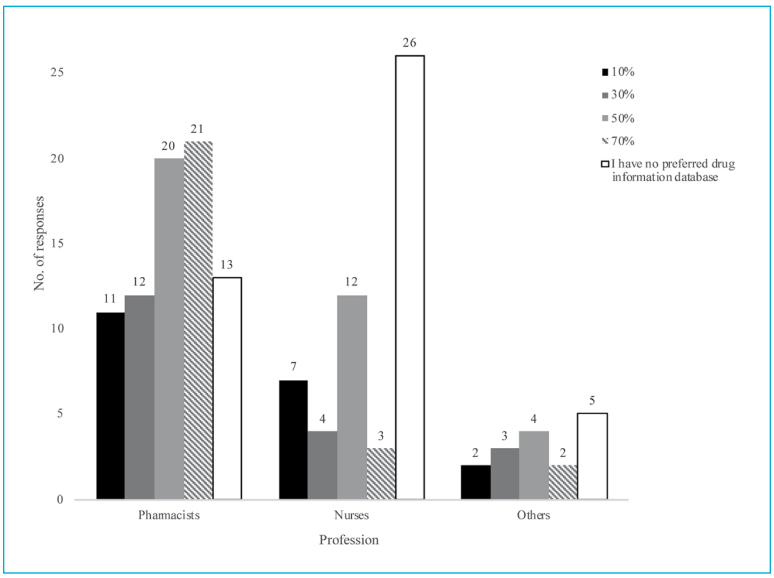

FIGURE 4. Distribution of each health professional's willingness to switch from preferred database, by percent cost reduction (n = 145).

DISCUSSION

With the rising number of new medications in the 21st century, online drug information databases have become a necessity for health professionals in the provision of patient care. In the face of budget constraints, the health authorities in the Lower Mainland of British Columbia can subscribe to only a single electronic drug information database at any given time. These subscriptions are contract-based and require periodic renewal, typically every 3 to 5 years. Contract renewal often presents an opportunity for the health authorities to re-evaluate the performance of the current drug information database and determine whether it still meets the needs of health professionals. It is also a chance to investigate any new and improved databases on the market. Cost is undoubtedly a major consideration in the subscription decision, but user preferences and other factors should be taken into account as well. Therefore, as a program evaluation study, we created an online survey with the primary objective of determining the main factors that health authority staff in the Lower Mainland consider when choosing a web-based drug information database. These factors are essentially timeless, such that decision-makers can refer to our findings again in 3 to 5 years' time, when the next contract ends. In addition, with free trial access to the web-based Micromedex database available to health authorities during the study period, our secondary objective was to determine health professionals' preference between the Lexicomp and Micromedex databases.

Drug information databases evolve over time, so having an up-to-date list of factors that health professionals consider when choosing a web-based drug information database can be valuable for decision-makers. In a study published in 2005, Galt and others[2] found that physicians listed frequency of update, ease of use, degree of usefulness, and drug reaction information as the most heavily weighted indicators in choice of a database. In a study published in 2008, Gettig[7] concluded that health professionals, including pharmacists, physicians, and nurses, deemed trustworthiness and accuracy as the 2 most important elements of a drug information database. Our study augments this previous literature because our survey was open to all health professionals, and we found that, consistent across all professions, ease of use and dosing information were the 2 leading factors considered in selecting a drug information database. Our results parallel those of Galt and others[2] by showing not only that content (such as drug dosing information) is important in a drug information database, but also that users place heavy emphasis on technical aspects (such as ease of use). Decision-makers may want to consider scoring both content and technical aspects when they are choosing between online drug information databases for future subscriptions.

Health authorities in the Lower Mainland of British Columbia have been subscribing to the Lexicomp product for the past 6 years, with the exception of the Provincial Health Services Authority, which has held subscriptions to both Lexicomp and Micromedex. Therefore, only some health professionals are familiar with both databases. However, the recent availability of free access to the Micromedex database for the Lower Mainland health authorities permitted all health professionals to test both databases. Previous studies have had conflicting results regarding health professionals' perspectives toward Lexicomp and Micromedex. Among 8 studies conducted between 2002 and 2017, Lexicomp was the preferred drug information database in

3 studies[2,5,8] and Micromedex was the database of choice in only 1 study.[9] In the 4 remaining studies,[10-13] the Lexicomp and Micromedex databases were found to be comparable, as we observed in the current study. In our side-by-side statistical comparison of the 2 databases, we found that the Lexicomp database was rated higher on technical aspects such as layout, navigation, and speed, whereas the Micromedex product was rated higher on content aspects such as sufficiency of information and ability to solve drug-related questions. These results matched previous findings that Lexicomp is easier to navigate whereas Micromedex has more detailed content.[2,10-12] Our results are important because they suggest to decision-makers that Lexicomp and Micromedex are currently comparable and that both meet the needs of health professionals.

To elaborate on the pharmacists' input to this study, we noticed a difference in responses between the question about overall quality of the database and the question about participants' overall database preference. We assumed that the database deemed to have better quality would also be the database preferred by most participants. To confirm this assumption, our survey purposely included the following 2 consecutive questions: "Which would you consider to be a drug information database with better quality?" and "If you only had access to one drug information database, which one would you prefer?" Most pharmacists picked Micromedex for the first question (concerning quality), but most pharmacists chose Lexicomp for the second question (concerning their personal preference). The increase in number of respondents who chose Lexicomp as the preferred database was mainly due to the 13 pharmacists who indicated in the first question that the 2 databases were of similar quality. When it comes to preferences, even though pharmacists thought Micromedex was the better-quality database, most preferred to use Lexicomp. Acknowledging participants' perceptions of Lexicomp as being superior to Micromedex in terms of its technical aspects, we can infer that pharmacists preferred Lexicomp because of its ease of use. With Lexicomp being the go-to resource in British Columbia for the past several years, participants may also have favoured the database that was more familiar.[14] The results of these 2 questions support our primary objective: not only is content accuracy important, but drug information databases should also be intuitively easy to operate.

When health authorities are subscribing to a drug information database, cost plays an important role. To evaluate the importance to health professionals of having access to their preferred drug information database, we asked participants about their willingness to switch to a less preferred database in relation to cost. Pharmacists most frequently chose 70% as the relative price reduction that would be required to justify a switch away from their preferred database, with a 50% reduction being the second-most frequent price point. In contrast, most other health professionals had no preference between the databases. Although the relative discount might have been different if we had provided actual cost data in the survey, we found the requested hypothetical discount somewhat informative for determining respondents' preferred electronic drug information database over an alternative. These results suggest that pharmacists are more particular about the resources they prefer to use; it is therefore important for pharmacists to have access to their preferred drug information database, because most were not willing to switch to a less-than-ideal database until it was 70% cheaper. Decision-makers should keep this in mind when deciding between databases in the future.

Strengths and Limitations

Our survey provided a summary of what some BC health professionals value in an online drug information database. The major strengths of this survey include its capability to illustrate health professionals' preference regarding the importance of drug content as well as user-friendliness in a drug information database. This survey was also one of the first to consult other BC health professionals, in addition to pharmacists, for their opinions about electronic drug information databases.

However, this evaluation had several limitations. The primary limitation was the response rate. We adopted a convenience sampling method, whereby the survey link was sent to directors or managers for further distribution to health professionals other than pharmacists; as such, the number of potential respondents reached was essentially unknown, and a response rate could not be calculated. In spite of this limitation, participants in this survey were similar, in terms of years of practice and primary roles in practice, to health professionals in British Columbia.[6] Nonetheless, future studies, with ability to calculate the response rate and efforts to encourage a high response rate, are recommended to improve the validity of our survey results and hence address the potential nonresponse bias of our study.

The design of our survey contributed to several limitations in our results. First, despite the online survey's capability to save partial responses, allowing participants to return later to pick up where they left off, we could not rule out the possibility that some participants repeated the survey; any duplicate responses would have interfered with the interpretation of our results. Second, participation in the survey was entirely voluntary, so the information captured would represent the participants who wanted their voices heard, resulting in potential sampling bias. Third, a discrepancy between the number of responses received (n = 247) and the number of surveys completed (n = 145) indicates a low completion rate, which may indicate that participants had trouble navigating the online survey. Fourth, we did not specify in the survey materials that it was our intention to seek participants' opinions about the web-based versions of

Micromedex and Lexicomp (not the app-based versions). It is unknown whether participants were answering the questions based on their experience with the web-based and/or the app-based drug information databases, although when interpreting our results, we assumed that participants were answering the questions based on experience with the web-based versions only. Fifth, for the cost question, we offered options in terms of relative cost reductions, instead of giving information about the actual cost of a drug information database. Although this approach improved the general applicability of our results for future subscription decisions, the results were highly subjective and might have been different if participants had been given known costs. Finally, we recognize that some health professionals had no prior experience with the Micromedex database, and their limited exposure to this database (through the trial access available during the study period) might have been too brief to allow accurate evaluation of their true preference between the 2 databases.

CONCLUSION

This is one of the first surveys showing that dosing information and ease of use were the 2 most influential factors for BC health professionals when deciding on an online drug information database. Study participants indicated no significant differences in usability, overall quality, and user preference between Micromedex and Lexicomp, the 2 most commonly subscribed databases by BC health authorities. Most pharmacists indicated that a database would have to be at least 70% cheaper than their preferred database to justify switching, whereas most other health professionals had no preference. These findings should be considered in future decisions about drug information database subscriptions.

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Yiu-Ching Jennifer Wong, PharmD, was, at the time this study was performed, a PharmD candidate (Class of 2020) in the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia. She is now a Pharmacy Resident with Lower Mainland Pharmacy Services in British Columbia.

Candy Lee, BSc(Pharm), ACPR, is a Clinical Pharmacist with Surrey Memorial Hospital, Surrey, British Columbia.

Adil Virani, BSc(Pharm), PharmD, FCSHP, is Manager of Pharmacy Services with Lower Mainland Pharmacy Services, and is also a Clinical Associate Professor with the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

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Address correspondence to:
Dr Yiu-Ching Jennifer Wong
Department of Pharmacy Services
Surrey Memorial Hospital
13750 96th Avenue
Surrey BC V3V 1Z2

e-mail: Jenniferwongyc@alumni.ubc.ca

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Clinical Blood Isolates from Hemodialysis Patients: Distribution of Organisms and Antimicrobial Resistance, 2007–2014

Courtney K Lawrence, Chris Sathianathan, Mauro Verrelli, Philippe Lagacé-Wiens, Robert Ariano, Grace Badejo, Michelle L Boyce, J Christine Davis, and Sheryl A Zelenitsky

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ABSTRACT

Background: Given the morbidity and mortality associated with bloodstream infections in hemodialysis patients, understanding the microbiology is essential to optimizing treatment in this high-risk population.

Objectives: To conduct a retrospective surveillance study of clinical blood isolates from adult hemodialysis patients, and to predict the microbiological coverage of empiric therapies for bloodstream infections in this population.

Methods: Clinical blood isolate data were collected from the 4 main outpatient hemodialysis units in Winnipeg, Manitoba, from 2007 to 2014. The distribution of organisms and antimicrobial susceptibilities were characterized. When appropriate, changes over time were tested using time series analysis. Study data were used to predict and compare the microbiological coverage of various empiric therapies for bloodstream infections in hemodialysis patients.

Results: The estimated annual number of patients receiving chronic hemodialysis increased steadily over the study period ($p < 0.001$), whereas the number of blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 ($p = 0.04$). Gram-positive bacteria represented 72.6% (743/1024) of isolates, including *Staphylococcus aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (23.1%, 237/1024). Only 26.1% (267/1024) of the isolates were gram-negative bacteria, the majority Enterobacteriaceae. The overall rate of methicillin resistance in *S. aureus* was 17.5%, and although annual rates were variable, there was a significant increase over time ($p = 0.04$). Antibiotic resistance in gram-negative bacteria was relatively low, except in *Escherichia coli*, where 13.5% and 16.2% of isolates were resistant to ceftriaxone and ciprofloxacin, respectively. Empiric therapy with vancomycin plus an agent for gram-negative coverage was predicted to cover 98.8% to 99.7% of blood isolates from hemodialysis patients, whereas cefazolin plus an agent for gram-negative coverage would cover only 67.5% to 68.4%.

Conclusions: In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the hemodialysis population.

Keywords: hemodialysis, microbiology, surveillance, resistance, antimicrobial stewardship

RÉSUMÉ

Contexte : Étant donné la morbidité et la mortalité associées aux infections du sang parmi les patients en hémodialyse, la compréhension de la microbiologie est essentielle à l'optimisation du traitement de cette population exposée à un risque élevé.

Objectifs : Mener une étude de surveillance rétrospective des isolats de sang cliniques des patients adultes en hémodialyse et prédire la couverture microbiologique des thérapies empiriques contre les infections du sang dans cette population.

Méthodes : Les données relatives aux isolats de sang cliniques ont été recueillies dans les quatre unités ambulatoires principales d'hémodialyse à Winnipeg (Manitoba), entre 2007 et 2014. La caractérisation a porté sur la distribution des organismes et les susceptibilités aux antimicrobiens. L'évolution dans le temps a été testée au besoin à l'aide d'une analyse chronologique. Les données de l'étude ont permis de prédire et de comparer la couverture microbiologique de diverses thérapies empiriques contre les infections du sang pour les patients en hémodialyse.

Résultats : On estime que le nombre annuel de patients recevant une hémodialyse chronique a augmenté régulièrement au cours de la période de l'étude ($p < 0{,}001$); le nombre d'isolats de sang a tout d'abord augmenté, puis il a grandement diminué : de 180 en 2011, il est passé à 93 en 2014 ($p = 0{,}04$). Les bactéries à Gram positif représentaient 72,6 % (743/1024) des isolats, y compris les *Staphylococcus aureus* (36,9 %, 378/1024) et les staphylocoques à coagulase négative (23,1 %, 237/1024). Seulement 26,1 % (267/1024) des isolats étaient des bactéries à Gram négatif, la majorité desquelles étant des Enterobacteriaceae. Le taux général de résistance à la méticilline de *S. aureus* était de 17,5 %, et bien que les taux annuels étaient variables, une augmentation importante a été observée avec le temps ($p = 0{,}04$). La résistance aux antibiotiques des bactéries à Gram négatif était relativement faible, sauf *Escherichia coli,* où respectivement 13,5 % et 16,2 % des isolats étaient résistants à la ceftriaxone et à la ciprofloxacine. On prévoyait que la thérapie empirique à la vancomycine associée à un agent pour la couverture à Gram positif couvrirait de 98,8 % à 99,7 % des isolats de sang des patients en hémodialyse, tandis que la céfazoline associée à un agent de la couverture à Gram négatif ne couvrirait que 67,5 % à 68,4 %.

Conclusions : À une époque qui se caractérise par une augmentation de la résistance aux antimicrobiens, des données comme celles-ci et celles portant sur la surveillance continue sont des composantes essentielles de la bonne gestion de l'utilisation des antimicrobiens pour les patients adultes en hémodialyse.

Mots-clés : hémodialyse, microbiologie, surveillance, résistance, gestion de l'utilisation des antimicrobiens

INTRODUCTION

Infectious diseases are associated with significant morbidity and are the second leading cause of death among patients receiving hemodialysis (HD).[1] Notable risk factors for infection include comorbidities (e.g., diabetes), immunosuppression associated with renal disease, and the requirement for vascular access.[2] Bloodstream infections in HD patients can also lead to serious complications such as septic thrombosis, osteomyelitis, and endocarditis.[3] In general, the treatment of bloodstream infections in this population is associated with high failure rates, poor clinical outcomes, and substantial health care costs.[4]

It is important to understand the microbiology of infections in high-risk populations where antimicrobial resistance rates and emerging trends can inform the selection of empiric therapy. Such surveillance is especially relevant in HD patients given their regular contact with health care settings, high rates of infection, and frequent use of antibiotics.[4,5] Bloodstream infections in HD patients are most often associated with gram-positive skin flora, followed by gram-negative bacteria and occasionally yeast.[2] The more common pathogens in this population are associated with resistance concerns such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), extended-spectrum β-lactamase-producing (ESBL) Enterobacteriaceae, and multidrug-resistant *Pseudomonas* spp. and *Acinetobacter* spp.[6,7] Clinical practice guidelines for the management of intravascular catheter–related infections in HD patients are broad, recommending "vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (e.g., third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination)" and cefazolin as an alternative to vancomycin in units with a low prevalence of MRSA.[8]

Despite the value of microbiological surveillance, studies in HD patients are limited,[2,4,9,10] and there are no current data for Canada. Our primary objective was to conduct a retrospective surveillance study of clinical blood isolates from the 4 main HD units serving adult patients in Winnipeg, Manitoba, from 2007 to 2014. The secondary objective was to use these data to predict the microbiological coverage of empiric therapies for bloodstream infections in the HD population.

METHODS

Surveillance data of clinical blood isolates from the 4 main outpatient HD units serving adult patients in Winnipeg, Manitoba, from January 2007 to December 2014 were extracted from the provincial microbiology information system (Delphic LIS, Auckland, New Zealand). Because the data were not linked to individual patients, research ethics approval was not required. During the study period, the 4 main HD units—the Sherbrook Centre Dialysis Unit and Central Dialysis Unit in the Health Sciences Centre, St Boniface Hospital Dialysis Unit, and Seven Oaks Hospital Dialysis Unit—served approximately 68% of patients receiving chronic HD in the Manitoba Renal Program.

Information on each clinical blood isolate was documented, specifically the date, location (HD unit), vascular site, organism identification, and antimicrobial susceptibilities. Importantly, these data excluded likely contaminants such as skin flora, unless culture results were positive in 2 sets of blood samples. Given the de-identified nature of surveillance data, additional steps were taken to exclude duplicate isolates (i.e., those with identical susceptibilities collected from different vascular sites at the same time in the same HD unit).[8]

The clinical blood isolates were characterized, and the distribution of organisms was detailed. Trends in the annual number of clinical isolates relative to the estimated number of HD patients were tested using a time series analysis with the Mann–Kendall trend test ($\alpha = 0.05$). Antimicrobial susceptibility rates were determined for the most common and clinically relevant pathogens (e.g., resistance concerns). Trends in antimicrobial resistance were also tested using time series analysis when the sample size exceeded 10 isolates of an organism in each year. All statistical analyses were conducted using SYSTAT 13 (Systat Software Inc., San Jose California).

The study data were used to predict the microbiological coverage of various empiric therapies for bloodstream infections in HD patients. The predictions were based on our distribution of clinical blood isolates for organisms with at least 15 isolates. Empiric regimens were selected based on the aforementioned clinical practice guidelines and included vancomycin or cefazolin plus ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin, tobramycin, or gentamicin for gram-negative coverage.[8] The predicted coverage of each empiric regimen was calculated by weighting the likelihood of each organism and summing the percentage of isolates susceptible to each antibiotic.

RESULTS

A total of 1024 clinical blood isolates (from 953 blood cultures) met the inclusion criteria. Of these isolates, the largest percentage were gram-positive bacteria (72.6%, 743/1024), followed by gram-negative bacteria (26.1%, 267/1024) and yeast (1.4%, 14/1024). Most blood cultures (93.2%, 888/953) contained a single isolate. While the estimated annual number of patients receiving chronic HD increased steadily over the study period ($p < 0.001$), the annual number of clinical blood isolates increased initially, then decreased significantly, from 180 in 2011 to 93 in 2014 ($p = 0.04$) (Figure 1). This trend was largely explained by a reduction in gram-positive bacterial isolates. As detailed in Table 1, staphylococci accounted for

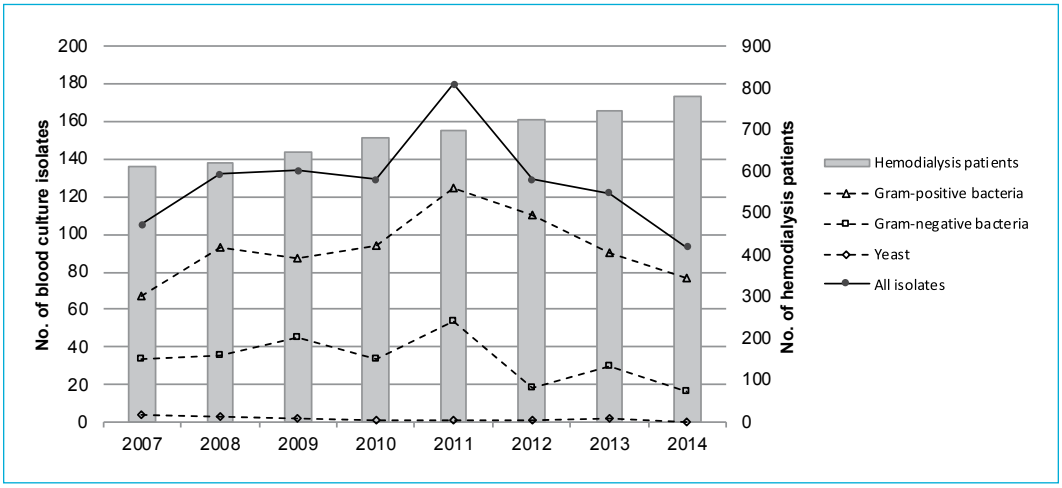

FIGURE 1. Annual number of clinical blood isolates and estimated annual number of patients receiving chronic hemodialysis, 2007 to 2014.

60.1% (615/1024) of clinical blood isolates, including *S. aureus* (36.9%, 378/1024) and coagulase-negative staphylococci (CoNS; 23.1%, 237/1024). The most common gram-negative bacteria were *Enterobacter* spp. (4.5%, 46/1024), *Klebsiella* spp. (4.2%, 43/1024), and *Escherichia coli* (3.6%, 37/1024).

Antimicrobial susceptibility data are shown in Table 2. The overall rate of oxacillin (methicillin) resistance in *S. aureus* (i.e., MRSA) was 17.5% (66/378), with a significant upward trend from 6.7% (2/30) in 2007 to 26.0% (13/50) in 2014 (p = 0.04) (Figure 2). The overall rate of oxacillin (methicillin) resistance in CoNS was 64.6% (153/237), but annual rates were variable with no notable trend over time (Figure 2). Only 2 VRE isolates (both *Enterococcus faecium*) were identified during the study. All gram-negative bacteria except *E. coli* had susceptibility rates above 90% for the third-generation cephalosporins, piperacillin-tazobactam, meropenem, ciprofloxacin, gentamicin, and tobramycin. For *E. coli*, ceftriaxone and ceftazidime resistance was identified in 13.5% (5/37) and 10.8% (4/37) of isolates, respectively, including 2 isolates that were ESBL producers. *Escherichia coli* also had the highest rate of ciprofloxacin resistance among the gram-negative bacteria (16.2%, 6/37).

The predicted microbiological coverage of empiric therapies was based on the current study's distribution of staphylococci, *Enterococcus faecalis*, *E. faecium*, *Streptococcus* spp., *Klebsiella* spp., *E. coli*, *Enterobacter* spp., *Serratia* spp., *Pseudomonas* spp., and *Acinetobacter* spp., which accounted for 88.1% (902/1024) of all isolates. The combinations of vancomycin with any of the agents for gram-negative coverage were predicted to cover 98.8% to 99.7% of the clinical blood isolates, whereas cefazolin plus an agent for gram-negative coverage would cover 67.5% to 68.4%. There were no differences based on the gram-negative coverage, whereby meropenem would cover less than 1% more isolates than ceftazidime, piperacillin-tazobactam, ciprofloxacin, tobramycin, or gentamicin.

TABLE 1. Distribution of Clinical Blood Isolates, 2007–2014

Organism	No. of Isolates* (n = 1024)	% of Isolates*
Gram-positive bacteria		
Staphylococcus spp.	615	60.1
S. aureus	(378)	(36.9)
S. epidermidis	(182)	(17.8)
Other CoNS†	(55)	(5.4)
Enterococcus spp.	59	5.8
E. faecalis	(45)	(4.4)
E. faecium	(12)	(1.2)
Streptococcus spp.	31	3.0
Other	38	3.7
Gram-negative bacteria		
Enterobacter spp.	46	4.5
E. cloacae	(35)	(3.4)
Klebsiella spp.	43	4.2
K. pneumoniae	(29)	(2.8)
Escherichia coli	37	3.6
Pseudomonas spp.	35	3.4
P. aeruginosa	(29)	(2.8)
Acinetobacter spp.	19	1.9
A. baumannii	(8)	(0.8)
Serratia spp.	19	1.9
Other	68	6.6
Yeast		
Candida spp.	14	1.4

*Isolate numbers and percentages for individual species are shown within parentheses.
†Coagulase-negative staphylococci other than *S. epidermidis*.

DISCUSSION

The current study provides important information about the microbiology of clinical blood isolates from HD patients over 8 years in Manitoba. There was a steady increase in the number of patients receiving chronic HD, whereas the number of isolates peaked in 2011 and then declined significantly. The reason for a spike in the number of isolates in 2011 is unclear. As expected, gram-positive bacteria accounted for most blood isolates (72.6%), followed by gram-negative bacteria (26.1%), and yeast (1.4%). In comparison, a CANWARD study of clinical blood isolates from hospitalized patients reported distributions of 51% and 46% for gram-positive and gram-negative bacteria, respectively.[11] Whereas *S. aureus* was the most common organism in HD patients (i.e., 36.9% in our study compared with 7.7% in CANWARD), *E. coli* was most prevalent in hospitalized patients (i.e., 22.6% in CANWARD compared with 3.6% in our study).[11]

Notably, our distribution of blood isolates was similar to reports of clinically confirmed bloodstream infections in HD patients from Australia (2008–2015),[4] the United States (2007–2011 and 2014),[2,9] and Denmark (1995–2010).[10] The percentages of *S. aureus* (36.9%) and CoNS (23.1%) in our

TABLE 2. Antimicrobial Susceptibilities of Clinical Blood Isolates, 2007–2014

Isolate	No. of isolates*	Susceptibility (%)										
		Oxacillin	Ampicillin	Vancomycin	Cefazolin	Ceftriaxone	Ceftazidime	Piperacillin-tazobactam	Meropenem	Ciprofloxacin	Gentamicin	Tobramycin
S. aureus	378	82.5	–	100	–	–	–	–	–	–	–	–
S. epidermidis	182	31.3	–	100	–	–	–	–	–	–	–	–
Other CoNS†	55	49.1	–	100	–	–	–	–	–	–	–	–
E. faecalis	45	–	91.1	100	–	–	–	–	–	–	–	–
E. faecium	12	–	16.7	83.3	–	–	–	–	–	–	–	–
Enterobacter spp.	46	–	–	–	–	–	–	97.8	100	100	100	100
Klebsiella spp.	43	–	–	–	88.4	100	100	100	100	100	100	100
E. coli	37	–	–	–	75.7	86.5	89.2	94.6	100	83.8	94.6	94.4
Pseudomonas spp.	35	–	–	–	–	–	94.3	94.3	97.1	94.3	97.1	100
Acinetobacter spp.	19	–	–	–	–	–	94.7	100	100	94.7	100	100

*Number of isolates, except for tobramycin (for which numbers of isolates were as follows: 42 for *Enterobacter* spp., 41 for *Klebsiella* spp., 36 for *E. coli*, and 34 for *Pseudomonas* spp.).
†Coagulase-negative staphylococci other than *S. epidermidis*.

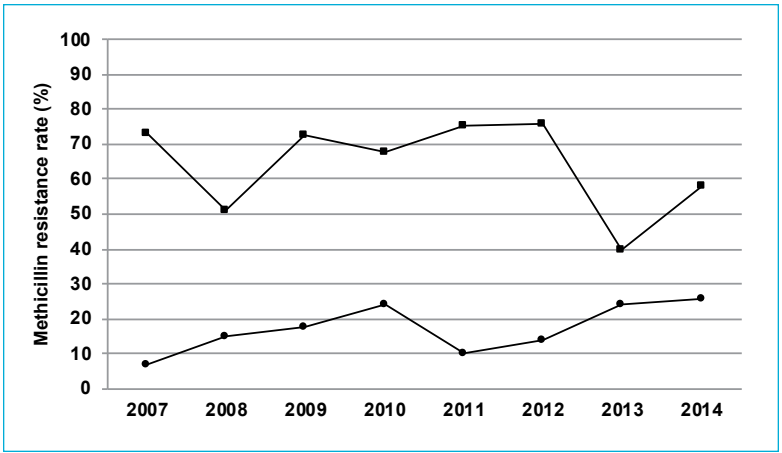

FIGURE 2. Rates of methicillin resistance in *Staphylococcus aureus* (n = 378, circles) and coagulase-negative staphylococci (n = 237, squares), 2007 to 2014.

study were also similar to their infection rates of 28% to 33% for *S. aureus* and 25% to 31% for CoNS.[2,4,9] Although our percentage of gram-negative bacteria was comparable to the aforementioned studies, *E. coli* was less common (3.6%) compared to the infection rates in Australia (8.1%)[4] and Denmark (12.6%).[10]

Our overall rate of methicillin resistance in *S. aureus* was 17.5%. This compared to 22.5% in clinical isolates (all specimen types) from hospitalized patients in Canada during the same time period.[12] Our increase in methicillin resistance from 6.7% in 2007 to 26.0% in 2014 is also consistent with a significant rise in community-acquired MRSA bloodstream infections observed in Canada between 2012 and 2017.[13] As expected, there was considerable geographic variability in MRSA resistance in clinically confirmed bloodstream infections in HD patients reported elsewhere, including none in Denmark (1995–2010),[10] 14% (2008–2015)[4] and 40% (2014)[2] in Australia, and 46% in the United States (2007–2011).[9] Our rate of vancomycin resistance in enterococci was only 3.4%, lower than the rates of 11.4% to 21.7% reported in those studies.[2,4,9] Our rate of ceftriaxone resistance in *E. coli* of 13.5% was comparable to theirs of 9% to 18%; our study was the only one to report ESBL status.[2,4,9] Despite global concerns about multidrug resistance in *Pseudomonas* spp. and *Acinetobacter* spp., there are limited susceptibility data in the HD population. Although our numbers were small, resistance rates for these organisms were relatively low compared with clinical blood isolates from hospitalized patients in Canada (the CANWARD study).[11]

Our predictions of microbiological coverage with empiric therapies showed that replacing vancomycin with cefazolin, in combination with an agent for gram-negative coverage, would reduce the overall coverage of clinical blood isolates in HD patients by more than 30%. Although our rate of methicillin resistance in *S. aureus* was only 17.5%, the high prevalence of methicillin resistance in CoNS (i.e., 64.6%) suggests that all staphylococcal pathogens should be considered to ensure appropriate empiric therapy. Conversely, there was no advantage to using the broader-spectrum agents such as piperacillin-tazobactam or meropenem to cover gram-negative pathogens. Our predictions also found that vancomycin plus ciprofloxacin would cover 98.8% of clinical blood isolates in HD patients, and may be an acceptable alternative for those with serious β-lactam allergy or aminoglycoside intolerance.

When interpreting the findings of the current study, it is important to consider the specific geographic context, particularly in terms of resistance rates. Even so, these data are informative and fill a notable gap in the study of infectious diseases in dialysis patients. Because our study was limited to the characterization of clinical blood isolates, not clinically confirmed infections, steps were taken to maintain clinical relevance by excluding duplicate cultures. Without access to patient identifiers, the possibility of repeat culture(s) of the same isolate on days following the index culture could not be ruled out. Therefore, the data were re-examined to identify the number of potential repeat isolates using a broad definition of the same organism, with identical susceptibilities, collected in the same HD unit within 7 days. According to this analysis, the number of possible repeats would not have exceeded 6% of all isolates. Our interpretation of some resistance patterns was limited by changes made to the cephalosporin and carbapenem susceptibility break points against Enterobacteriaceae and *Pseudomonas* spp. in 2012. Most importantly, continued surveillance in HD patients is needed to maintain the relevance of this initial work, particularly given the trends in methicillin resistance and the emergence of VRE and ESBL-producing organisms near the end of our study.

CONCLUSION

This study provides insight on the distribution of organisms and antimicrobial susceptibilities of clinical blood isolates from multiple HD units in Manitoba over 8 years. The large sample size allowed for a longitudinal analysis, which is rarely available for this patient population. In an era of increasing antimicrobial resistance, data such as these and ongoing surveillance are essential components of antimicrobial stewardship in the HD population.

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Courtney K Lawrence, BScPharm, is a PhD student with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Chris Sathianathan, MD, FRCPC, is a Nephrologist with the Manitoba Renal Program at St Boniface Hospital, and is also an Assistant Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Mauro Verrelli, BSc, MD, MHA, FRCPC, is a Nephrologist with the Manitoba Renal Program at St Boniface Hospital, and is also an Associate Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Philippe Lagacé-Wiens, MD, FRCPC, DTM&H, is a Medical Microbiologist with Clinical Microbiology, Diagnostic Services, Shared Health at St Boniface Hospital, and is also an Assistant Professor with the Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Robert Ariano, BScPharm, PharmD, is a Clinical Pharmacist at St Boniface Hospital and is also a Clinical Professor with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Grace Badejo, HBSc Microbiology, BScPharm, is a Community Pharmacist and Associate at Shoppers Drug Mart, Winnipeg, Manitoba.

Michelle L Boyce, BSc, BScPharm, ACPR, is a Hospital Pharmacist at the Ottawa Hospital, Ottawa, Ontario. At the time of this study, she was a candidate for the ACPR designation, which has now been conferred.

J Christine Davis, BScPharm, PharmD, ACPR, is a Clinical Pharmacist with the Manitoba Renal Program at St Boniface Hospital, and is also a Clinical Assistant Professor with the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Sheryl A Zelenitsky, BScPharm, PharmD, is a Professor in the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, and is also a Nil-Salaried Clinical Pharmacist with the St Boniface Hospital, Winnipeg, Manitoba.

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Address correspondence to:
Dr Sheryl Zelenitsky
College of Pharmacy, Rady Faculty of Health Sciences
University of Manitoba
750 McDermot Avenue
Winnipeg MB R3E 0T5

e-mail: zelenits@umanitoba.ca

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How Hospital Pharmacists Spend Their Time: A Work-Sampling Study

Daniel Wong, Andrea Feere, Vandad Yousefi, Nilufar Partovi, and Karen Dahri

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ABSTRACT

Background: The expanded scope of pharmacist practice allows for increased comprehensive care and improved patient outcomes at the cost of increased workload and time demands on pharmacists. There are limited descriptive metrics for the time that pharmacists spend on various activities during the workday. An evaluation of the time spent on different activities would allow for potential optimization of workflow, with a focus primarily on devoting more time to direct patient care activities.

Objective: To quantify the amount of time that hospital and clinic-based pharmacists spend on clinical activities, including direct and indirect patient care, and nonclinical activities.

Methods: An observational fixed-interval, work-sampling study was conducted at 2 hospitals, Vancouver General Hospital and Richmond Hospital, both in British Columbia. Trained observers followed individual pharmacists for a set period. The pharmacists' activities were recorded in 1-min increments and classified into various categories.

Results: In total, 2044 min of activity, involving 11 individual pharmacists, were observed. Clinical activities accounted for 82% of total time, 12% (251 min) on direct patient care activities and 70% (1434 min) on indirect patient care activities. The most common direct clinical activity was conducting patient medication history interviews (73 min; 4% of total time), and the most common indirect clinical activity was assessment and evaluation (585 min; 29%). The most common nonclinical activities were walking (91 min; 4% of total time), looking for something (57 min; 3%), and teaching pharmacy students on practicum (60 min; 3%).

Conclusions: Although the pharmacists spent most of their time on clinical activities, face-to-face time with patients (direct clinical activities) seemed low, which highlights an area for potential improvement. The pharmacists spent much more time documenting information in pharmacy-specific monitoring forms (i.e., assessment and evaluation) than they spent writing notes or recommendations in the chart, for sharing with other health care professionals.

Keywords: time, work sampling, pharmacist, activities

RÉSUMÉ

Contexte : L'élargissement du champ d'activité du pharmacien permet d'améliorer la qualité des soins et les résultats pour le patient au prix d'une augmentation de la charge et du temps de travail des pharmaciens. Il existe peu de mesures descriptives temps que les pharmaciens consacrent à leurs diverses activités de la journée. Une évaluation de ce temps permettrait d'optimiser le flux de travail afin que l'accent puisse être mis principalement sur l'augmentation du temps réservé aux activités de soins directs des patients.

Objectif : Quantifier le temps que passent les pharmaciens des hôpitaux et des cliniques à effectuer des activités cliniques, y compris des activités de soins directs et indirects, ainsi que des activités non cliniques.

Méthodes : Une étude observationnelle par échantillonnage à intervalles fixes a été menée dans deux hôpitaux : le Vancouver General Hospital et le Richmond Hospital, tous deux en Colombie-Britannique. Des observateurs formés ont suivi chaque pharmacien en particulier pendant une période déterminée. Leurs activités étaient consignées par tranches d'une minute et classées en diverses catégories.

Résultats : L'observation a porté sur des activités totalisant 2044 minutes réparties entre 11 pharmaciens. Les activités cliniques représentaient 82 % du temps total, 12 % (251 min) des activités étaient consacrées aux soins directs et 70 % (1434 min), aux soins indirects. L'activité clinique directe la plus courante consistait à mener des entrevues portant sur les antécédents pharmacothérapeutiques des patients (73 min, 4 % du temps total) et l'activité clinique indirecte la plus courante était l'évaluation (585 min, 29 %). Les activités non cliniques les plus courantes étaient la marche (91 min, 4 % du temps total), la recherche de quelque chose (57 min, 3 %) et la formation des étudiants stagiaires en pharmacie (60 min, 3 %).

Conclusions : Bien que les pharmaciens consacrent la plus grande partie de leur temps à des activités cliniques, le temps passé auprès des patients (activités cliniques directes) semblait faible, ce qui indique une possibilité d'amélioration. Les pharmaciens passent beaucoup plus de temps à consigner de l'information dans des formulaires de contrôle spécifiques à la pharmacie (c.-à-d. évaluation) qu'à rédiger des notes ou des recommandations dans les tableaux pour les partager avec les autres professionnels de la santé.

Mots-clés : temps, échantillon de travail, pharmacien, activités

INTRODUCTION

In the inpatient setting, pharmacist-initiated interventions have been associated with reductions in adverse drug events, improvements in medication adherence, and shortened hospital stays.[1] Since 2009, legislative changes at the federal and provincial levels have given rise to an expanded scope of practice for pharmacists in Canada.[2] As a result, pharmacists in both hospital and community settings are developing a more immersive role within the health care team and are now able to change drug dosages, make therapeutic substitutions, administer vaccines, order laboratory tests and evaluate their results, and initiate drug therapy.[2-5] This expanded scope of practice has resulted in improved patient outcomes, increased pharmacist job satisfaction (secondary to increased autonomy), and reduced health care costs.[5] However, the expansion of pharmacy practice has also increased demands on pharmacists' time. A survey evaluating the impact of expanded practice on hospital-based pharmacists in a single Canadian centre found that although these pharmacists were able to increase comprehensive patient care, they felt that lack of time was the greatest barrier to maximizing their expanded roles.[3,5] Evaluating how hospital pharmacists spend their time during the workday may allow identification of areas for increased efficiency.

Observational studies in Australia have previously evaluated how hospital-based pharmacists spend their working day. Investigators shadowed pharmacists to see what tasks they performed daily and to determine approximately how much time was spent on each task.[6-8] For example, deClifford and others[6] looked at the amount of time hospital pharmacists spent performing clinical and nonclinical activities to gather baseline data on the pharmacists' tasks. They found that 56% of total time was devoted to clinical activities, with the bulk of this time being spent on professional communication, chart reviews, and medication history interviews. Time spent on nonclinical activities included breaks, social activities, ordering drugs, and discharge dispensing. Similar results were observed in a time-sampling study comparing pharmacist productivity on wards with and without electronic medication management systems.[7] Medication chart review was the most frequently performed activity (35% and 36% of observed time, respectively, on wards with and without the electronic systems), followed by clinical review (18% and 14%, respectively).[7] Stuchbery and others[8] obtained different results when they recorded the activities of 6 clinical pharmacists over 3 days. They noted that medication order review was the most frequently recorded event (53.7% of total events), which suggested a greater emphasis on dispensary-related tasks.[8]

These divergent results suggest that a pharmacist's workday may be influenced by site-specific demands; however, differences in the definitions of clinical and nonclinical activities in previous studies may also account for the observed variation in results. Therefore, it is difficult to predict how these findings would apply to the work distribution of pharmacists practising at sites in Canada, or British Columbia specifically.

The objective of this observational study was to develop a better understanding of how hospital and clinic-based pharmacists spend their time, using a work-sampling methodology. To our knowledge, no such studies have been conducted to describe the work distribution of pharmacists in Canadian hospitals. By gaining a clearer sense of how much time is spent performing different activities, we aimed to obtain insights into whether efficiencies can be found to optimize pharmacists' utilization of their time.

METHODS

Design and Sampling

In this observational study, a fixed-interval, work-sampling methodology was used to assess the workflow of hospital and clinic-based pharmacists in 2 acute care institutions in British Columbia, Canada—Vancouver General Hospital and Richmond Hospital—over a 6-month period (March to August 2017). A similar approach has previously been used to study the workflow of other health care providers.[6-9] Vancouver General Hospital is a tertiary care centre with a staff that includes 50 pharmacists working on wards or clinics on any given day, whereas Richmond Hospital is a smaller community hospital, with 7 pharmacists working on wards or clinics daily. The pharmacists at both hospitals cover a variety of inpatient, outpatient, and critical care settings. Pharmacists may be employed in positions that are either entirely focused on the ward or clinic or entirely focused on dispensary duties, or their positions may involve a combination of both types of work.

These 2 hospitals, including their associated outpatient clinics, utilize a combination of electronic and paper-based documentation systems. The electronic computer system contains information about patient medications, laboratory values, diagnostic investigations, and physicians' transcriptions. The paper charts contain daily assessments and progress notes from physicians and the allied health team.

For this study, and more generally in the hospitals involved, clinical work was defined in accordance with the American College of Clinical Pharmacy's *Standards of Practice for Clinical Pharmacists*.[10] These standards of practice state that clinical pharmacists possess "accredited residency training or equivalent postlicensure experience" and perform medication management in team-based direct patient care environments.[10] Pharmacists working primarily in the dispensary, pharmacy assistants, and regulated pharmacy technicians who had limited clinical encounters with patients were therefore excluded. To focus on pharmacists working in clinical rather than dispensary roles,

pharmacists were observed only when they were scheduled for clinical shifts, such as providing direct patient care on inpatient units or in outpatient clinics.

A literature search was conducted to determine the various activities that could be captured through data collection.[6,8] The observable activities were categorized as clinical and nonclinical activities. Clinical activities were defined as any activities related to the clinical care of a patient, whereas nonclinical patient care activities were defined as activities with no relation to clinical care.[6,8] Ten major clinical activities were included, 4 classified as direct patient care activities and 6 classified as indirect patient care activities. In addition, there were 11 major nonclinical activities. The classification system is summarized in Box 1.

An e-mail invitation to participate in the study was sent out by the administrative staff at each site using group e-mail lists. In addition, an informational presentation was given at each site's monthly pharmacist staff meeting to recruit participants. Pharmacists could directly contact one of the investigators to enrol in the study. Ethics approval was obtained from the University of British Columbia Research Ethics Board, and all participants provided written informed consent.

No honorarium was given to the participants. At the time of enrolment, participants could indicate their preference for when the data collector would shadow them during a regular work shift. To prevent changes in work performance in the context of the study, only the observers (data collectors) had access to individual pharmacists' data. This was intended to maintain blinding and anonymity to other study investigators, who might be in a supervisory role in relation to the pharmacist participants.

Data Collection and Procedure

Pharmacists' activities were identified and recorded by 1 of 2 trained observers (D.W. or A.F.). Participating pharmacists chose the time and duration of observation during a single 8-h shift. The observers were third-year pharmacy students not employed by the hospitals. These observers completed a training session and a 1-h trial session together to become familiar with the activities performed by pharmacists, so that they could recognize and classify them according to the predetermined categories.

Using a 5E901 Ironman Triathlon watch (Timex), an observer recorded a participant's current activity on a paper activity log every minute, according to the predetermined categories and subcategories. If multiple tasks were performed within the same 1-min interval, the observer noted all tasks, but the task performed for most of the interval was used for data analysis. However, when participants spent more than 1 min performing different activities ("multitasking"), the activities were recorded in an alternating manner every minute until the multitasking ended. This approach was applied consistently to ensure equal representation of all activities performed simultaneously, while adhering to the once-per-minute observation protocol. If the

BOX 1. Categories of Activities Performed by Hospital Pharmacists

Clinical Activities
Direct
Patient medication history interview
Patient general interview
Patient medication counselling
  Specific drug product
  Discharge medications
Contacting other sources of information (family physician, patient's relatives) for collateral information

Indirect
Assessment and evaluation
  Review of patient chart
  Review of computer system
Patient care rounds
  Bedside rounds
  Paper rounds/"running the list" (medical team does a quick paper review of each patient's chart)
  Interdisciplinary rounds
Therapeutic interventions
  Direct recommendations (speaking with physician)
  Chart notes for recommendations
  Chart notes for documentation
Discharge coordination
  Writing discharge prescriptions, medication reconciliation on discharge
  Faxing prescriptions
  Obtaining health insurance coverage
    Pharmacare enrolment
    Special Authority approval
Dispensing
  Order entry and verification
  Checking/labelling product
Communication with staff
  Answering questions from ward staff
  Answering questions from physicians
  Returning pages, answering phone calls

Nonclinical Activities
Walking
Taking breaks
Performing self-care (using bathroom, washing hands)
Engaging in social activity (personal conversations with pharmacy or other staff)
Waiting for elevator
Looking for something
  Chart/medical record
  Staff
  Patient's own medications
  Patient
Communicating (checking e-mail)
Attending staff meetings
Attending educational presentations
Teaching pharmacy students on practicum
Other (photocopying, organizing patient charts, putting things away, logging out of computer system)

participant was speaking to other hospital staff, patients, or visitors in a situation requiring confidentiality, the observer waited at an appropriate distance and confirmed the nature of the activity afterward. In the event that the participant took a break during the observation period, only the start and end times of the break were noted. Time that the participant spent talking to the observer or introducing others to the observer was excluded from the analysis.

For instances where pharmacists participated in activities that did not fall within the predefined categories, the observers met after completion of all data collection to determine where to allocate any uncategorized minutes or whether it was necessary to create a new category. If the 2 observers could not reach an agreement, then they consulted one of the study investigators to reach a decision.

Data Analysis

All recorded activities were transferred to a digital spreadsheet (Microsoft Excel 2015, version 15.0, Microsoft Corporation). Simple descriptive statistics were then applied to determine which activities were performed most frequently and which activities consumed the most time for the pharmacists collectively.

RESULTS

The observers shadowed the participating pharmacists for a range of 1.5 to 4 consecutive hours in a 1:1 ratio. Data for a total of 2044 min (34.1 h) of activity were collected from 11 pharmacists: 1724 min (84%) from 8 pharmacists at Vancouver General Hospital and 320 min (16%) from 3 pharmacists at Richmond Hospital. These pharmacists worked in various areas of the hospitals: 4 in inpatient units, 3 in outpatient clinics, and 4 in critical care areas. All of the participating pharmacists had previously completed a hospital pharmacy residency, and 4 pharmacists had also completed a postgraduate Doctor of Pharmacy degree. Each participant was observed on average for 186 min (standard deviation 59 min) over a single uninterrupted observation period. Overall, 82% of the total time (1685 min) was spent doing clinical activities and 18% of the total time (359 min) was spent on nonclinical activities. Tables 1 and 2 show the breakdown of total time spent performing each type of activity (by category and subcategory).

Clinical Activities

The time spent performing clinical activities consisted of 251 min (12% of total time) for direct clinical activities and 1434 min (70% of total time) for indirect clinical activities. The most frequently observed indirect clinical activity, which was also the most frequently observed activity overall, was assessment and evaluation (585 min; 29% of total time). Participants spent most of that time reviewing various documents on the computer system (380 min; 19%), which involved activities such as assessing patients' current and past medications, accessing patient information, interpreting laboratory test results, and looking up drug information. Reviewing charts accounted for the remaining time spent on assessment and evaluation (205 min; 10%), and was often done while simultaneously reviewing other patient information on the computer system. It was also noted that during assessment and evaluation, participants frequently wrote notes in their own pharmacy-specific patient monitoring forms. Participants also spent a

TABLE 1. Time Spent by Hospital Pharmacists on Clinical Activities

Clinical Activity	Amount (%) of Time (min) (n = 2044)	
Direct	251	(12)
Patient medication history interview	73	(4)
Patient general interview	62	(3)
Patient medication counselling	65	(3)
Specific drug product	59	(3)
Discharge medications	6	(0.3)
Contacting other sources of information (family physician, patient's relatives) for collateral information	51	(2)
Indirect	1434	(70)
Assessment and evaluation	585	(29)
Review of patient chart	205	(10)
Review of computer system	380	(19)
Patient care rounds	466	(23)
Bedside rounds	258	(13)
Paper rounds/"running the list"	208	(10)
Interdisciplinary rounds	0	(0)
Therapeutic interventions	190	(9)
Direct recommendations (speaking with physician)	25	(1)
Chart notes for recommendations	65	(3)
Chart notes for documentation	100	(5)
Discharge coordination	61	(3)
Writing discharge prescriptions, medication reconciliation on discharge	35	(2)
Faxing prescriptions	9	(0.4)
Obtaining health insurance coverage: Pharmacare enrolment	3	(0.1)
Obtaining health insurance coverage: Special Authority approval	14	(1)
Dispensing	10	(0.5)
Order entry and verification	8	(0.4)
Checking/labelling product	2	(0.1)
Communicating with staff	122	(6)
Answering questions from ward staff	72	(4)
Answering questions from physicians	27	(1)
Returning pages, answering phone calls	23	(1)

substantial proportion of their time attending patient care rounds (466 min; 23%), which consisted of bedside rounds (258 min; 13%) and paper rounds (208 min; 10%). Participants spent 9% (190 min) of total time making therapeutic interventions, such as documenting clinical notes in patient charts (100 min; 5%).

Nonclinical Activities

The most time-consuming nonclinical activities were walking and looking for things; however, these activities accounted for only 4% (91 min) and 3% (57 min) of total time, respectively. When participants were looking for things, it was most often a patient chart that was being sought (38 min; 2%). Participants spent 5% of their overall time participating in educational activities, such as attending presentations (47 min; 2%) and teaching students on practicum (60 min; 3%). Breaks and checking e-mails accounted for 2% (39 min) and 1% (21 min) of participants' total time, respectively.

Post Hoc Analysis of Inpatient and Outpatient Pharmacists

A subset of the participants (n = 3) were identified as working in outpatient units. We therefore conducted a post hoc analysis to determine if there were any differences in clinical activity levels between the inpatient and outpatient environments. A total of 1513 min of activity were observed in inpatient units compared with 531 min of activity in outpatient units. Inpatient pharmacists spent 85% (1291 min) of inpatient time on clinical activities, whereas outpatient pharmacists spent 74% (394 min) of outpatient time on clinical activities. However, within the clinical activity category, the outpatient pharmacists spent 28% (147 min) of their total time on direct clinical activities, namely counselling about drug products and conducting general interviews with patients. In contrast, the inpatient pharmacists spent only 7% (104 min) of their total time on direct clinical activities. The inpatient pharmacists spent most of their clinical time on indirect activities, such as reviewing patient charts and the computer system.

TABLE 2. Time Spent by Hospital Pharmacists on Nonclinical Activities

Nonclinical Activity	Amount (%) of Time (min) (n = 2044)	
All	359	(18)
Walking	91	(4)
Taking breaks	39	(2)
Performing self-care (using bathroom, washing hands)	18	(1)
Engaging in social activity (personal conversations)	13	(1)
Waiting for elevator	6	(0.3)
Looking for something	57	(3)
Chart/medical record	38	(2)
Staff	4	(0.2)
Patient's own medications	0	(0)
Patient	15	(1)
Communicating (checking e-mail)	21	(1)
Attending staff meetings	0	(0)
Attending educational presentations	47	(2)
Teaching students on practicum	60	(3)
Other*	7	(0.3)

*Photocopying, organizing charts, putting things away, logging out of the computer system.

DISCUSSION

The purpose of this study was to quantify the amount of time that hospital pharmacists spent on various activities and to determine if there are any efficiencies that could be introduced to hospital practice to allow pharmacists to perform more clinical activities rather than nonclinical activities. Our findings suggest that the pharmacists already spend considerably more time performing clinical activities than nonclinical activities (82% versus 18%), especially relative to other time-sampling studies.[6] For example, in their time-sampling study in Australia, deClifford and others[6] found that hospital pharmacists participated in clinical activities 56% of the time, leaving 44% for nonclinical activities.

Despite the large proportion of time spent on clinical activities, we found that only 12% of total time was spent on direct clinical activities, that is, activities involving direct interactions with patients or caregivers. As valued members of the patient care team, with a rapidly evolving role, pharmacists may have a greater impact by spending more time collaborating with the team and interacting with patients. Regardless of how the role of pharmacists evolves, time spent working directly with patients should remain a priority. Not only might this improve patients' awareness of the role of hospital pharmacists, but it might also increase pharmacists' contributions to the team in areas such as educating patients about their medications, optimizing therapy for efficacy, and minimizing adverse effects of medications. As professionals with highly drug-focused education, pharmacists may gather information and monitor specific parameters that might not have been considered by others. For example, when taking a medication history, a pharmacist may probe into the specifics of a drug interaction, adverse drug reaction, or drug allergy that might not be as thoroughly investigated by others, whether because of lack of time or different priorities. We believe that this is a mechanism whereby increased face-to-face time with patients may yield more discoveries of information that could significantly affect prescribing decisions.

We also found that pharmacists spent a considerable amount of time (29%) on assessment and evaluation: copying laboratory values, medication details, drug levels, and other information from the computer system and paper chart into a pharmacy-specific patient monitoring form used by pharmacy staff for patient follow-up. In comparison, only 8% of total time was spent writing chart notes to share recommendations or documentation with physicians and other health care professionals. It might be beneficial for other health care professionals if pharmacists could allocate more time to documenting their clinical findings and interventions in the patient's permanent health care record rather than the department's own monitoring form. By doing so, pharmacists could showcase their unique assessments with other members of the health care team, providing input for future clinical decisions and documenting their work for others to see.

Pharmacy technicians may also be of great utility in optimizing the workload of pharmacists. For example, they may be in the best position to assist pharmacists by reorganizing and preparing patient charts before pharmacists begin to review patients and before rounds. Nearly one-third of pharmacists' time was spent assessing patient charts and the online system and recording their own notes (i.e., assessment and evaluation), but technicians could accelerate this routine process by compiling all relevant photocopies and print-outs of pertinent resources for a given patient in one folder. Pharmacists would then have access to all required documentation in one location and might therefore be able to allocate more time to working directly with patients and the medical team.

When the existing paper chart system eventually transitions to an electronic system, pharmacists will have direct access to all of the patient information that is currently contained in a mix of paper-based and electronic charting systems. Lo and others[7] found that the average amount of time required for completing review activities (e.g., medication chart, clinical data, pathology results) was significantly reduced when pharmacists employed electronic medication management systems on the ward. It might therefore be fruitful to repeat a work-sampling study after implementation to assess whether there are any changes in direct clinical activities in these 2 Canadian hospitals.

Although our subanalysis comparing outpatient and inpatient pharmacists involved small sample sizes, it highlighted a notable difference in the type of work that these pharmacists perform daily. As might have been expected, the outpatient pharmacists spent much more time on direct clinical activities than their inpatient counterparts. Interestingly, the inpatient pharmacists spent a large amount of time on indirect clinical activities, which suggests that these participants were driving the numbers in the overall results. However, given the small and uneven amount of data comparing inpatient and outpatient pharmacists, the information is only hypothesis-generating. A larger comparative study is needed to better understand how workflow differs between these different areas of practice.

Despite the use of established methodology for conducting time-sampling studies, there were some limitations to this study. Because of the relatively small sample size, it is difficult to generalize our findings to hospital pharmacy practice more generally. Having an observer constantly present did not allow for a true naturalistic observation of the pharmacists. Additionally, to increase participation, pharmacists were allowed to select a scheduled time at their own convenience for shadowing and observation. This may have skewed our sample to feature more clinical activities. We likely did not capture all of the time that pharmacists spent on breaks and at staff meetings because we observed only a portion of each participant's day. Only one of the pharmacists who participated in the study was serving as a preceptor for a pharmacy student on rotation, so our data are likely not reflective of how much time pharmacists actually spend teaching. For future time-sampling studies, it is recommended that each pharmacist be observed for the entirety of one shift to accurately gauge the various activities performed from the beginning to the end of the shift. Perhaps one contributing reason why deClifford and others[6] found that pharmacists spent only 56% of their time on clinical activities was that they observed pharmacists over entire working days. The 56% value would equate to nearly 4 h of clinical activities, assuming an 8-h shift with a 60-min lunch break. If we theoretically factor a 60-min break into our results and assume the same proportion of clinical activities during the working hours, we would expect to see approximately 5 h and 45 min spent on clinical activities per 8-h shift, which would reduce the proportion of clinical activities from 82% to 72%. Finally, we noted that minimal time was allocated to walking and looking for things, but this may be attributed to the location-based staffing system in the hospitals studied. In other hospitals where staff coverage is more dispersed, more time may be spent on these activities.

CONCLUSION

This study revealed that pharmacists already spend a significant amount of time performing clinical activities, although most of that time was devoted to indirect clinical activities. It would be worthwhile for future studies to investigate the proportion of time spent in face-to-face interactions between pharmacists and patients, and to observe a larger sample of hospital pharmacists, perhaps through the inclusion of more hospitals. As pharmacy practice continues to evolve, such studies may further illuminate where pharmacists' time is being spent and could be used to determine how to maintain the current emphasis on direct patient care activities over indirect activities.

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Daniel Wong, BSc(Pharm), ACPR, is a Clinical Pharmacist with the Royal Columbian Hospital, New Westminster, British Columbia.

Andrea Feere, BSc(Pharm), ACPR, is a Clinical Pharmacist with the Abbotsford Regional Hospital and Cancer Centre, Abbotsford, British Columbia.

Vandad Yousefi, MD, CCFP FHM, is a Hospitalist with the Vancouver General Hospital, Vancouver, British Columbia.

Nilufar Partovi, BSc(Pharm), PharmD, FCSHP, is Coordinator of Clinical Pharmacy Services with the Vancouver General Hospital, University of British Columbia Hospital, and the G F Strong Rehabilitation Centre and is also a Clinical Professor with the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

Karen Dahri, BSc(Pharm), ACPR, PharmD, FCSHP is a Clinical Pharmacotherapeutic and Research Specialist with the Vancouver General Hospital and Assistant Professor (Partner) with the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

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Address correspondence to:
Dr Karen Dahri
Vancouver General Hospital
855 West 12th Avenue
Vancouver BC V5Z 1M9

e-mail: Karen.Dahri@vch.ca

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Chemotherapy in the Intensive Care Unit: An Evaluation of Context and Outcomes

Salmaan Kanji, Erica MacLean, Farah Joy Rashid, Michelle Pittman, Melanie Trinacty, David Allan, and Erin Rosenberg, on behalf of the Resource Optimization Network

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ABSTRACT

Background: Administration of chemotherapy to highly vulnerable, critically ill patients in the intensive care unit (ICU) is becoming more common, but the process requires significantly more resources than chemotherapy administration in specialized oncology settings.

Objective: To describe the context, complications, and outcomes of chemotherapy administration for cancer-related indications in ICU patients.

Methods: For this retrospective observational study, consecutive patients receiving parenteral chemotherapy in the ICU at the General Campus of The Ottawa Hospital between January 1, 2014, and December 31, 2017, were identified using pharmacy records. The clinical characteristics of these patients, details of their chemotherapy regimens, and outcomes were analyzed.

Results: A total of 32 patients were included in the study. Of these, 27 patients (84%) had a hematological malignancy, 16 (50%) had a documented infection at the time of chemotherapy administration, and 29 (91%) received their first cycle of chemotherapy on an urgent basis during the ICU admission rather than as a scheduled or planned treatment. Severity of illness was high both at ICU admission and at the time of chemotherapy treatment; regimen modifications, drug interactions, and adverse events were common. Remission and survival data were available for 28 patients at 12 months. Eighteen (56%) of the 32 patients survived to hospital discharge, and 12 (38%) survived to 6 months; at 12 months, survival was 25% (7 of 28 patients with available data). About one-quarter of the patients were in remission at 6 and 12 months.

Conclusion: Administering chemotherapy in the ICU is feasible, but the process is resource-intensive. Patients with aggressive hematological cancers who require treatment on an urgent basis represent the most commonly observed scenario. This study highlights the complexity of management and the importance of multidisciplinary care teams for this patient population.

Keywords: critical care, chemotherapy, cancer

RÉSUMÉ

Contexte : L'administration de chimiothérapie à des patients hautement vulnérables et gravement malades admis dans une unité de soins intensifs (USI) est de plus en plus courante, mais le processus exige beaucoup plus de ressources que dans des environnements spécialisés en oncologie.

Objectif : Décrire le contexte, les complications et les résultats de l'administration de chimiothérapie pour les indications liées au cancer de patients admis dans une USI.

Méthodes : Les patients successifs ayant participé à cette étude observationnelle rétrospective, qui recevaient une chimiothérapie parentérale dans une USI du Campus général de l'Hôpital d'Ottawa entre le 1er janvier 2014 et le 31 décembre 2017, ont été déterminés à l'aide de dossiers de pharmacie. Les caractéristiques cliniques de ces patients, les détails de leur programme de chimiothérapie ainsi que les résultats ont fait l'objet d'une analyse.

Résultats : Trente-deux (32) patients ont été inclus dans l'étude. Parmi eux, 27 (84 %) souffraient d'une hémopathie maligne, 16 (50 %) avaient une infection documentée au moment de l'administration de la chimiothérapie et 29 (91 %) recevaient en urgence le premier cycle de chimiothérapie pendant leur admission à l'USI plutôt que sous forme de traitement programmé ou planifié. Étant donné l'extrême gravité de la maladie lors de l'admission à l'USI et du traitement de chimiothérapie de ces patients, les modifications apportées au programme, les interactions médicamenteuses et les effets secondaires étaient fréquents. Les données relatives à la rémission et à la survie à 12 mois de 28 patients étaient disponibles. Le congé hospitalier a été donné à 18 (56 %) patients survivants sur les 32 admis et 12 (38 %) survivaient au 6e mois, alors qu'au 12e mois, le taux de survie était de 25 % (7 des 28 patients dont les données étaient disponibles). Environ un quart des patients étaient en rémission au 6e et au 12e mois.

Conclusion : L'administration de chimiothérapie dans une USI est faisable, mais le processus exige beaucoup de ressources. Les patients atteints d'un cancer hématologique agressif qui ont besoin en urgence d'un traitement constituent le scénario le plus courant. Cette étude souligne la complexité de la gestion et l'importance des équipes de soins multidisciplinaires pour cette population de patients.

Mots-clés : soins intensifs, chimiothérapie, cancer

INTRODUCTION

Cancer prevalence is increasing, and new treatments are being developed that are prolonging life and improving the chance of cure. One consequence of this phenomenon is that cancer patients are requiring care in the intensive care unit (ICU) with increasing frequency: for postoperative care after major surgical resection, for chemotherapy- and radiation-related complications, and for concurrent critical illness.[1] Not only are ICU clinicians encountering more critically ill cancer patients in this setting, but they are being called upon more frequently to administer systemic chemotherapy in the ICU. The literature describing the context, risks, barriers, clinical considerations, and patient outcomes associated with treating cancer in the ICU is sparse.[1,2]

At The Ottawa Hospital, ICU nurses and most other members of the clinical team have no formal training in chemotherapy administration or monitoring. The process of administering chemotherapy in the ICU requires a multidisciplinary approach involving intensivists, hematologists/oncologists, nurses, and pharmacists. ICU staff use protocols and checklists to coordinate consulting services for cancer management, including writing and checking chemotherapy orders, making dose adjustments for end-organ dysfunction, actually administering the chemotherapy, and disposing of cytotoxic materials. Because ICU nurses are not certified to administer chemotherapy, the current policy requires that a certified oncology nurse come to the ICU to administer the systemic treatment and dispose of cytotoxic materials afterward. Despite this "hands-off" approach, ICU staff are required to anticipate, identify, and manage complications related to both the cancer itself and the cancer treatment.

A search of the literature identified only 4 small studies of chemotherapy administration for the treatment of cancer in the ICU.[3-6] These studies ranged in size from 37 to 100 patients, with none of them being conducted in North America.[3-6] The purpose of the current study was to describe the context, complications, and outcomes of administering chemotherapy for cancer-related indications to ICU patients.

METHODS

This retrospective observational study was conducted at the General Campus of The Ottawa Hospital, an acute tertiary care centre in Ottawa, Ontario. The Ottawa Hospital serves the adult population in the Champlain Local Health Integration Network, which comprises 1.3 million residents in the Ottawa area. Ethics approval for this chart review was received from the Ottawa Health Science Network Research Ethics Board (protocol 20180088-01H).

Consecutive patients admitted to the ICU who received parenteral chemotherapy for treatment of malignancy from January 1, 2014, to December 31, 2017, were identified from pharmacy records; the pharmacy-generated list was double-checked via hand searching of written chemotherapy orders. Receipt of systemic chemotherapy in the ICU was confirmed by a review of patients' medical records. Patients were excluded if the systemic chemotherapy was not administered intravenously, if the treatment consisted only of biologic or antibody therapy (e.g., rituximab), or if the treatment was not administered for a cancer indication.

Data were collected from patients' medical records. Baseline characteristics collected included age, sex, and reason for ICU admission (according to Acute Physiology and Chronic Health Evaluation [APACHE] III disease groupings[7]). Data collected to describe the indication and types of chemotherapy administered included type of malignancy, chemotherapy regimen and its intent (curative or palliative; scheduled or urgent), cycle of the current regimen, number of previous chemotherapy regimens received for the same indication, regimen modifications, dose adjustments, and prophylaxis received for tumour lysis syndrome (allopurinol or rasburicase).[8] Hematological malignancies were recorded by grade, where acute myelogenous leukemia, acute lymphoblastic leukemia, and high-grade non-Hodgkin lymphoma were classified as high-grade, and other types of hematological malignancies were classified as low-grade.[3,9] Solid organ tumours were described as stage I to IV or in terms of local versus extensive disease. Data describing the severity of illness both at ICU admission and at the time of chemotherapy administration included APACHE II scores,[10,11] RIFLE (risk, injury, failure, loss, end-stage renal disease) criteria[12] (assessed using urine output), need for renal replacement therapy, documented infection (positive culture results up to 1 week before chemotherapy administration and/or receipt of systemic antibiotic or antifungal therapy, excluding prophylaxis with sulfamethoxazole-trimethoprim, acyclovir, or fluconazole and empiric ceftriaxone), Sequential Organ Failure Assessment (SOFA) scores,[13] white blood cell count, neutrophil count (with neutropenia defined as an absolute neutrophil count less than 1.5×10^9/L),[14] platelet count (with severe thrombocytopenia defined as platelet count less than 50×10^9/L),[15] liver enzymes, bilirubin, and Richmond Agitation-Sedation Scale (RASS) score.[16] The frequency and severity of chemotherapy-related complications were described by collecting data on the presence of tumour lysis syndrome (identified according to prespecified definition of laboratory and clinical values[8]), presence of renal failure 7 days after treatment (using the RIFLE criteria),[12] and hepatotoxicity 7 days after treatment (defined as an increase in liver enzymes and/or bilirubin to more than 3 times baseline, with baseline values determined from pre–ICU admission bloodwork when available [most patients], and otherwise based on the first measured values from the index hospital admission).[17] Other complications that we considered were

febrile neutropenia up to 4 weeks after chemotherapy or discharge from hospital, duration of neutropenia, delay of the current chemotherapy cycle, and drug interactions involving the chemotherapy agent.[18]

The outcomes of interest included survival at the time of ICU discharge and hospital discharge, 6- and 12-month survival, and 6- and 12-month remission. Survival and remission were adjudicated by 2 clinicians (F.J.R., M.P.), and disagreements were settled by a third (D.A.). ICU and hospital lengths of stay, as well as duration of mechanical ventilation, were also collected.

Data are presented in tabular format, using measures of central tendency and dispersion, as appropriate, for all patients and also for subgroups of hospital survivors (those who survived to hospital discharge) and hospital nonsurvivors (those who did not survive to hospital discharge). No statistical comparisons between groups were planned or performed.

RESULTS

Over the 4-year study period, 175 patients were identified as having a prescription for parenteral chemotherapy in the ICU. Of these, 143 patients were excluded (Figure 1). Thirty-two patients met the inclusion criteria and were included in the analysis (8, 8, 5, and 11 patients in calendar years 2014, 2015, 2016, and 2017, respectively). The demographic characteristics of the patients are presented in Table 1. The most common reason for ICU admission was respiratory-related (n = 21, 66%), followed by cardiovascular/vascular (n = 3, 9%), hematologic (n = 3, 9%), and metabolic (n = 2, 6%). Eighteen patients (56%) survived to ICU and hospital discharge. All 14 patients who died in hospital died in the ICU. Most patients (n = 27, 84%) had diagnosis of a hematological malignancy for which they received chemotherapy (Table 2). Most patients had a high-grade hematological malignancy or stage 4 solid tumour malignancy.

The severity of illness at ICU admission and at the time of chemotherapy administration is described in Table 3. All patients were critically ill at ICU admission, with a mean APACHE II score of 20.3 (standard deviation [SD] 9.3). The median duration between ICU admission and chemotherapy administration was 1 day, with a range from 0 to 22 days; therefore, the markers of severity of illness were similar at the time of ICU admission and the time of chemotherapy administration. Organ failure was common in this patient population at the time of ICU admission, with mean SOFA score of 8.8 (SD 4.3) and more than 30% of patients described as having some degree of renal dysfunction, according to the RIFLE criteria. Patients' critical illness is further supported by the presence of documented infection, with 15 (47%) of the patients having a documented infection at ICU admission and 16 (50%) at the time of chemotherapy administration, the most common site of infection being the lung. Ten (67%) of the 15 patients with documented infection at the time of ICU admission did not survive to hospital discharge.

Most patients (n = 29, 91%) received their first cycle of chemotherapy in the ICU, with 23 (72%) of the regimens having a curative intent (Table 4). We determined that 30 (94%) of the patients received chemotherapy in an urgent manner. Eight (25%) of the patients had regimen modifications (most commonly for reduced functional status), whereas 7 (22%) had dose reductions to accommodate organ dysfunction. The median number of drug interactions involving at least 1 chemotherapeutic agent was 1.5, with a range from 0 to 7. These drug interactions were identified retrospectively to help describe the complexity of care for patients in this study and had a risk rating of C (alert to monitor) or D

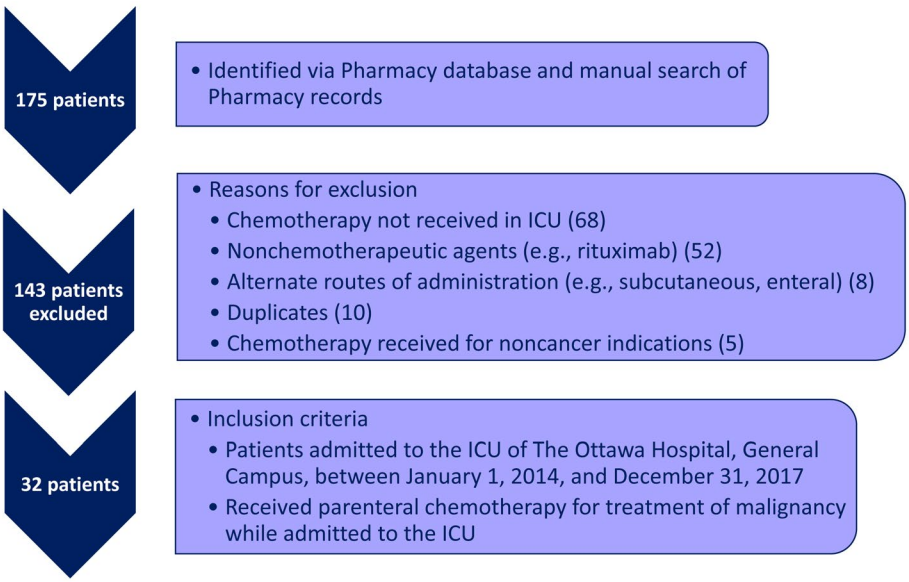

FIGURE 1. Patient recruitment. ICU = intensive care unit.

TABLE 1. Demographic Characteristics of Patients

Characteristic	Patient Group; No. (%) of Patients*		
	All (*n* = 32)	Hospital Survivors (*n* = 18)	Hospital Nonsurvivors (*n* = 14)
Sex, male	14 (44)	10 (56)	4 (29)
Age (years) (mean ± SD)	55.6 ± 14.5	52.4 ± 15.2	55.1 ± 13.9
Reason for ICU admission			
Cardiovascular/vascular	3 (9)	1 (6)	2 (14)
Respiratory	21 (66)	10 (56)	11 (79)
Neurologic	1 (3)	1 (6)	0 (0)
Sepsis	1 (3)	1 (6)	0 (0)
Metabolic	2 (6)	2 (11)	0 (0)
Hematologic	3 (9)	2 (11)	1 (7)
Unknown	1 (3)	1 (6)	0 (0)

ICU = intensive care unit, SD = standard deviation.
*Except where indicated otherwise.

TABLE 2. Types of Cancer

Type of Cancer	Patient Group; No. (%) of Patients		
	All (*n* = 32)	Hospital Survivors (*n* = 18)	Hospital Nonsurvivors (*n* = 14)
Hematological	27 (84)	15 (83)	12 (86)
High-grade malignancy	22/27 (81)	11 (61)	11 (79)
Low-grade malignancy	5/27 (19)	4 (22)	1 (7)
Acute leukemia	11/27 (41)	4 (22)	7 (50)
Lymphoma	15/27 (56)	11 (61)	4 (29)
Multiple myeloma	1/27 (4)	0 (0)	1 (7)
Solid tumour	5 (16)	3 (17)	2 (14)
Small cell carcinoma of lung	3/5 (60)	2 (11)	1 (7)
Ovarian cancer	1/5 (20)	0 (0)	1 (7)
Non-seminoma, germ cell tumour	1/5 (20)	1 (6)	0 (0)

(consider therapy modification).[18] Patients received a variety of chemotherapy regimens, with most patients receiving a regimen containing 3 or more components.

Twelve-month survival and remission data were available for 28 patients at the time of study completion (Table 5). Outcome data were missing for the other 4 patients because they were lost to follow-up or because there was inadequate documentation for outcome adjudication at 6 and 12 months. Twelve patients (38%) survived to the 6-month time point and 7 (25%) survived to 12 months. Among survivors, 47% (8/17) achieved remission at 6 months, and 50% (7 /14) achieved remission at 12 months. Overall, 14 patients (44%) in the study population experienced clinical or laboratory tumour lysis syndrome, and 14 patients (44%) experienced febrile neutropenia.

Numerically, more nonsurvivors had been admitted to the ICU for respiratory failure, and they received deeper sedation, as measured by RASS scores. Nonsurvivors also had more documented infections (mostly lung infections) at the time of chemotherapy administration, relative to hospital survivors. Compared with survivors, nonsurvivors had shorter ICU and hospital lengths of stay but longer duration of mechanical ventilation. Also, fewer nonsurvivors experienced tumour lysis syndrome and hepatotoxicity, but more had renal dysfunction 7 days after receiving their chemotherapy.

DISCUSSION

Chemotherapy administration in the ICU is a high-risk intervention that requires each member of a large multidisciplinary team to play a key role to ensure that patients receive safe and effective treatment. We sought to describe the context of chemotherapy administration in the ICU for the treatment of malignancy and the outcomes of these patients. In this study, most of the cancer patients who

TABLE 3. Severity of Illness

Severity	Patient Group; No. (%) of Patients*					
	All (*n* = 32)		Hospital Survivors (*n* = 18)		Hospital Nonsurvivors (*n* = 14)	
	At ICU Admission	At Chemotherapy Administration	At ICU Admission	At Chemotherapy Administration	At ICU Admission	At Chemotherapy Administration
APACHE II score (mean ± SD)	20.3 ± 9.3	19.5 ± 8.0	20.4 ± 9.4	19.4 ± 8.6	20.1 ± 7.2	19.6 ± 7.6
SOFA score (mean ± SD)	8.8 ± 4.3	8.9 ± 4.6	9.4 ± 4.9	9.6 ± 4.8	8.0 ± 3.4	8.1 ± 4.4
RIFLE criteria						
No dysfunction	21 (66)	22 (69)	12 (67)	14 (78)	9 (64)	8 (57)
Risk	6 (19)	2 (6)	4 (22)	0 (0)	2 (14)	2 (14)
Injury	1 (3)	3 (9)	0 (0)	1 (6)	1 (7)	2 (14)
Failure	4 (12)	5 (16)	2 (11)	3 (17)	2 (14)	2 (14)
Loss	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
End-stage renal disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Receiving renal replacement therapy	2 (6)	3 (9)	2 (11)	3 (17)	0 (0)	0 (0)
Documented infection	15 (47)	16 (50)	5 (28)	7 (39)	10 (71)	9 (64)
Blood	2 (6)	2 (6)	0 (0)	1 (6)	2 (14)	1 (7)
Lung	9 (28)	9 (28)	3 (17)	2 (11)	6 (43)	7 (50)
Urine	3 (9)	2 (6)	1 (6)	1 (6)	2 (14)	1 (7)
Skin and soft tissue	1 (3)	1 (3)	1 (6)	1 (6)	0 (0)	0 (0)
Gastrointestinal	0 (0)	2 (6)	0 (0)	2 (11)	0 (0)	0 (0)
Neutropenia	6 (19)	8 (25)	4 (22)	5 (28)	2 (14)	3 (21)
Thrombocytopenia	13 (41)	14 (44)	8 (44)	8 (44)	5 (36)	6 (43)
Liver SOFA score (median and range)	0 (0 to 4)	1 (0 to 4)	1 (0 to 4)	1 (0 to 4)	0 (0 to 3)	0 (0 to 4)
Renal SOFA score (median and range)	0 (0 to 4)	0 (0 to 3)	0 (0 to 4)	0 (0 to 3)	0 (0 to 3)	0.5 (0 to 3)
RASS score (median and range)	–3 (–5 to 1)	–3 (–5 to 1)	–1.5 (–5 to 0)	–1.5 (–5 to 0)	–3 (–5 to 1)	–3.5 (–5 to 0)

APACHE = Acute Physiology and Chronic Health Evaluation; RASS = Richmond Agitation-Sedation Scale (scores range from –5 [unarousable] to +4 [combative]); RIFLE = risk, injury, failure, loss, end-stage renal disease; SD = standard deviation; SOFA= Sequential Organ Failure Assessment (scores range from 0 to 4, where higher numbers indicate greater organ dysfunction).
*Except where indicated otherwise.

received chemotherapy in the ICU had a hematological malignancy. For a large number of patients, this was their first treatment, and it was required on an urgent basis because of high severity of illness and/or extent of disease. Few patients had significant renal or hepatic dysfunction; however, one-quarter of patients required dose reductions, and one-quarter required modifications of treatment regimens. The patients' severity of illness was high, both at admission and at the time of chemotherapy administration. Half of the patients had a documented infection that was being treated at the time of chemotherapy administration. Overall, survival rates in this study were in keeping with previously reported survival rates for patients with aggressive hematological malignancies.[19]

Although a formal comparison of survivors and nonsurvivors was beyond the scope of this study, it is interesting to note that, at least numerically, nonsurvivors were more likely to receive chemotherapy in the ICU for palliative intent, were more likely to have active infections at the time of chemotherapy administration, were less likely to experience tumour lysis syndrome, and ultimately had shorter hospital and ICU stays but longer duration of mechanical ventilation when compared with survivors. While these all appear to be logical observations, more nonsurvivors than survivors experienced some degree of renal dysfunction but less hepatotoxicity after chemotherapy, which is more difficult to explain. The observation that active infection was more often present in nonsurvivors at the time of chemotherapy administration may represent an opportunity for quality improvement initiatives, with acknowledgement that balancing the risks of delaying urgent treatment for the underlying malignancy likely also has consequences. However, in cases where delaying chemotherapy by a week or two is possible, it may be an approach worth considering, to allow completion of treatment of concomitant infections. Given the limitations associated with our sample size, we

TABLE 4. Characteristics of Chemotherapy Regimens

Characteristic	Patient Group; No. (%) of Patients*		
	All (*n* = 32)	Hospital Survivors (*n* = 18)	Hospital Nonsurvivors (*n* = 14)
Time from ICU admission to chemotherapy administration (days) (median and range)	1 (0–22)	2 (0–22)	0 (0–12)
First cycle of chemotherapy given in the ICU	29 (91)	18 (100)	11 (79)
Intent of chemotherapy			
Palliative	9 (28)	4 (22)	5 (36)
Curative	23 (72)	14 (78)	9 (64)
Intent of cycle			
Scheduled	2 (6)	0 (0)	2 (14)
Urgent	30 (94)	18 (100)	12 (86)
Received previous chemotherapy regimens for same malignancy	3 (9)	2 (11)	1 (7)
Regimen modification	8 (25)	5 (28)	3 (21)
Dose reduction	7 (22)	4 (22)	3 (21)
Drug interactions† per patient (median and range)	1.5 (0–7)	1 (0–7)	2 (0–7)
C-level interactions (median and range)	1 (0–5)	1 (0–5)	2 (0–5)
D-level interactions (median and range)	0 (0–3)	0 (0–2)	0 (0–3)
Use of G-CSF	12 (38)	5 (28)	7 (50)
Use of TLS prophylaxis	25 (78)	15 (83)	10 (71)
Chemotherapy regimen			
CHOP ± R, CHOP modified	11 (34)	7 (39)	4 (29)
Carboplatin-containing regimens: CarboEtop, CarboTaxol	3 (9)	1 (6)	2 (14)
Single agent: HD MTX, cytarabine, doxorubicin, vincristine	5 (16)	2 (11)	3 (21)
Leukemia (re)induction: IDAC, MEC	4 (13)	1 (6)	3 (21)
CVAD A/1	2 (6)	1 (6)	1 (7)
CVP ± R	4 (13)	4 (22)	0 (0)
Other: BEP (3 days), VD PACE, Cis75Etop	3 (9)	2 (11)	1 (7)

BEP = bleomycin + etoposide + cisplatin; CarboEtop = carboplatin + etoposide; CarboTaxol = carboplatin + paclitaxel; CHOP ± R = cyclophosphamide + doxorubicin + vincristine + prednisone ± rituximab; Cis75Etop = cisplatin + etoposide; CVAD = cyclophosphamide + vincristine + doxorubicin + dexamethasone; CVP ± R = cyclophosphamide + vincristine + prednisone ± rituximab; G-CSF = granulocyte colony-stimulating factor; HD MTX = high-dose methotrexate; ICU = intensive care unit; IDAC = idarubicin + cytarabine; MEC = mitoxantrone + etoposide + cytarabine; TLS = tumour lysis syndrome; VD PACE = bortezomib + dexamethasone + platinum agent + doxorubicin + cyclophosphamide + etoposide.

*Except where indicated otherwise.

†C-level interactions = alert to monitor; D-level interactions = consider therapy modification.

caution against the over-interpretation of these comparisons but would suggest that future investigations explore some of these associations.

Care requirements were also complex in this patient population, given the frequency of end-organ dysfunction requiring dose modifications, drug interactions, and adverse events. Most patients received chemotherapy regimens involving 3 or more drugs, which is associated with a higher resource burden in most cases. For example, for a patient receiving the regimen CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), a certified nurse must be present to administer 3 IV medications, which can take upwards of an hour.

Three other retrospective observational studies have been conducted in similar fashion. One study, completed by Benoit and others,[3] involved patients with hematological malignancies who received (or were intended to receive) chemotherapy in the ICU. The size of their study sample was comparable to ours, at 37 patients. They found that only ventilation during the ICU stay was associated with in-hospital mortality among patients who received chemotherapy. Our study findings were comparable to theirs, with the majority of patients in both studies having high-grade hematological malignancies, similar numbers of patients having active infection at the time of chemotherapy administration, and similar rates of in-hospital mortality. Song

TABLE 5. Outcomes

Outcome	Patient Group; No. (%) of Patients*		
	All (*n* = 32)	Hospital Survivors (*n* = 18)	Hospital Nonsurvivors (*n* = 14)
Length of ICU admission (days) (median and range)	9.5 (3–47)	10.5 (4–47)	8 (3–37)
Length of hospital admission (days) (median and range)	23.5 (6–342)	28 (9–342)	16.5 (6–95)
Survival			
At ICU discharge	18 (56)	18 (100)	0 (0)
At 6 months	12 (38)	12 (67)	0 (0)
At 12 months†	7/28 (25)	7/14 (50)	0 (0)
Remission			
At 6 months†	8/31 (26)	8/17 (47)	0 (0)
At 12 months†	7/28 (25)	7/14 (50)	0 (0)
Length of mechanical ventilation (days) (median and range)	5 (0–35)	4.5 (0–35)	7.5 (0–34)
Tumour lysis syndrome			
Laboratory	7 (22)	5 (28)	2 (14)
Clinical	7 (22)	5 (28)	2 (14)
RIFLE criteria, 7 days after treatment			
No dysfunction	24 (75)	15 (83)	9 (64)
Risk	2 (6)	2 (11)	0 (0)
Injury	3 (9)	0 (0)	3 (21)
Failure	3 (9)	1 (6)	2 (14)
Loss	0 (0)	0 (0)	0 (0)
End-stage renal disease	0 (0)	0 (0)	0 (0)
Hepatotoxicity, 7 days after treatment	3 (9)	3 (17)	0 (0)
Febrile neutropenia after chemotherapy			
Present	14 (44)	8 (44)	6 (43)
Duration (days) (median and range)	2 (0–16)	3.5 (0–14)	2 (0–16)

ICU = intensive care unit; RIFLE = risk, injury, failure, loss, end-stage renal disease.
*Except where indicated otherwise.
†Denominator indicates the number of patients for whom data were available at the specified time point.

and others[5] conducted another study in patients with hematological or solid tumour malignancies who received chemotherapy in the ICU. The degree of organ failure and the occurrence of respiratory failure requiring mechanical ventilation were both independent predictors of mortality in this study, whereas degree of organ involvement, disease status, and extent of underlying malignancy were not shown to have an impact on mortality. Similar to our study, the majority of patients had diagnosis of a hematological malignancy and were being treated for their first presentation of disease, and the time to onset of treatment and ICU mortality rate were the same. The final study with a study design similar to that of the current study was conducted by Wohlfarth and others.[6] Their retrospective observational study included 56 patients with hematological or solid tumor malignancies, among whom survival was associated with independent factors of age, comorbidity, severity of acute illness, septic shock, vasopressor use, and renal replacement therapy. The rate of hospital survival, the frequency of hematological malignancies, and the reason for admission to the ICU were similar to the current study, but the overall rate of tumour lysis syndrome was lower.

Administering chemotherapy in the ICU adds complexity to an already complex environment. Because ICU nurses are not certified to administer chemotherapy, a nurse from the oncology unit, with appropriate certification, must be available to administer the drugs. Given that most patients received 3 or more agents in their regimen, there can be many issues with staffing and coordination of care. Upwards of 15 health care professionals may be involved in the many steps of this process, which not only creates a more complex task but also adds logistical and safety issues. The hematologist/oncologist, in consultation with the ICU clinical team, is often responsible for making the decision to treat the patient and is also responsible for writing the chemotherapy order. Pharmacists from both hematology/oncology and critical care review the written order for accuracy and make dose modifications

for end-organ dysfunction as required. They also coordinate the logistical processes related to scheduling times of administration and preparation of the medication by pharmacy technicians, taking into account the fact that some drugs have a very short period of stability. Nursing staff are heavily involved throughout the entire process. The ICU nurse is responsible for ensuring that all parties are notified that an order has been written, while care facilitators and clinical care leaders from both the ICU and oncology/hematology coordinate the availability of a certified nurse who can come to the ICU to administer the chemotherapy. This nurse, along with the pharmacist, educates the bedside nurses about monitoring for adverse events and administration of complementary therapies (e.g., antinauseants, hydration). The ICU medical team is still primarily responsible for the patient's overall care, including monitoring for adverse events and treatment outcomes. Because this process involves many people and tasks, algorithms and checklists are used to minimize errors and ensure the process unfolds as efficiently as possible. One consideration to minimize the number of participants in a patient's circle of care would be to maintain a limited number of chemotherapy-trained ICU nurses. The challenge would then be to ensure that these specialized ICU nurses are available for patients needing to receive chemotherapy and to have a contingency plan for when they are not available. There would also be concerns about maintaining skills, given that chemotherapy administration in the ICU is relatively infrequent.

We identified and made efforts to mitigate the limitations associated with this study. Because of the retrospective nature of the study design, data collection was limited by documentation and what was available in the electronic record; however, we encountered less than 1% missing data. We relied on a pharmacy database to generate the list of patients who met the inclusion criteria. To minimize the risk of missing eligible patients and ensure completeness of our sample, we further verified the patient list by hand-sorting through all written chemotherapy orders for the study period. Given the nature of select data points that were collected and the possibility of interpretation, we developed an adjudication process, whereby 3 clinical experts who were members of the patients' care circles and who had access to alternative forms of information helped to determine select outcomes. Another limitation relates to generalizability to a larger population, given that the study was conducted in a single-centre ICU; however, we can confirm that this was the only ICU to administer chemotherapy in the Champlain LHIN. Therefore, any patients treated through The Ottawa Hospital and included in this study would not have received chemotherapy in the ICU of any other hospital (if they had, such treatment could potentially have affected their outcomes). Given the small number of patients in this study, we were unable to make any statements about predictors of mortality; however, the results do provide an idea of issues that may be experienced with patients admitted to the ICU. Finally, this cohort of patients represents only a subset of the patients who receive chemotherapeutic agents in the ICU; other ICU patients may receive biologic agents such as rituximab for a variety of indications, may receive chemotherapy via different routes (e.g., enteral, subcutaneous), or may receive chemotherapy for noncancer indications (e.g., cyclophosphamide for vasculitis). The procedures and policies described in this paper apply only to patients in the ICU receiving IV chemotherapy for cancer indications. In all other scenarios, the processes of drug prescription, delivery, administration, and monitoring are less well defined.

CONCLUSION

In this retrospective observational study, administration of chemotherapy in the ICU was most commonly employed for treatment for hematological malignancies; a variety of regimens were used. Severity of illness was both evident and similar at the time of ICU admission and the time of chemotherapy administration. In this study population, complexity of care was high because of end-organ dysfunction, drug interactions, and concomitant critical illness, including high rates of active infection. Chemotherapy-related adverse events and mortality were high. This study highlights the complexity of managing care for these patients and the importance of multidisciplinary care teams.

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Salmaan Kanji, PharmD, is with The Ottawa Hospital and the Ottawa Hospital Research Institute, Ottawa, Ontario.

Erica MacLean, BScPharm, is with The Ottawa Hospital, Ottawa, Ontario.

Farah Joy Rashid, BScPharm, is with The Ottawa Hospital, Ottawa, Ontario.

Michelle Pittman, BScPharm, is with The Ottawa Hospital, Ottawa, Ontario.

Melanie Trinacty, BScPharm, is with The Ottawa Hospital, Ottawa, Ontario.

David Allan, MD, FRCPC, is with The Ottawa Hospital and the Ottawa Hospital Research Institute, Ottawa, Ontario.

Erin Rosenberg, MD, MHA, FRCPC, is with The Ottawa Hospital, Ottawa, Ontario.

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Address correspondence to:
Dr Salmaan Kanji
The Ottawa Hospital and Ottawa Hospital Research Institute
501 Smyth Road
Ottawa ON K1H 8L6

e-mail: skanji@toh.ca

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Osmolality of Medications Administered in the Neonatal Intensive Care Unit

The most recent recommendations regarding enteral feeding solutions for newborns state that they should have a maximum osmolality of 450 mOsm/kg (400 mOsm/L) and that the use of hyperosmolar feeding solutions may be a factor in the development of necrotizing enterocolitis.[1,2] These recommendations are based on historical consensus,[3] and there is little other evidence to guide this practice. For preterm newborns at risk of necrotizing enterocolitis, or infants at risk of osmotic diarrhea because of gastrointestinal abnormalities, enteral medications are often diluted in small amounts of breast milk or formula (usual osmolality about 300 mOsm/kg), both for ease of administration and to reduce the osmolar challenge of the medications. Unfortunately, for many compounded and commercially available oral liquid medications, published osmolality values are not available to clinicians to aid in assessing the osmolar load and the risks associated with enteral administration. The purpose of this study was to measure the osmolality of several proprietary and compounded medications commonly used in the neonatal intensive care unit.

We performed an analytically controlled laboratory study to measure the osmolality of 23 medications, specifically 8 proprietary and 15 compounded medications (Table 1).[4–11] Osmolality was measured with a Micro OSMETTE II model 6002 osmometer (Precision Systems, Natick, Massachusetts), calibrated with aqueous normal sodium chloride in triplicate. The maximum measurable osmolality was 2000 mOsm/kg; medications with higher osmolality were diluted 1:1 or 1:2 with distilled water before measurement, and the resulting osmolality was multiplied by 2 (for 1:1 dilutions) or 3 (for 1:2 dilutions). Osmolality was measured in 2 aliquots of each medication (from the same lot). We planned to measure a third time if 2 osmolality measurements differed by more than 10 mOsm/kg, but this did not occur.

The measured osmolality of the proprietary medications ranged from 624 mOsm/kg to 7480 mOsm/kg, and that of the compounded medications ranged from 25 mOsm/kg to 3385 mOsm/kg (Table 1). Only 3 of the 23 medications had osmolality below the recommended maximum 450 mOsm/kg:

TABLE 1. Osmolality of Commercially Available and Compounded Medications for Neonates

Drug Name and Concentration	Manufacturer	Osmolality (mOsm/kg)
Commercially available		
Digoxin (Toloxin), 0.05 mg/mL	Pendopharm	3670
Fluconazole, 10 mg/mL	Pfizer Canada	2020
Ibuprofen liquid (infant's Motrin, dye-free, berry flavour), 40 mg/mL	McNeil Consumer Healthcare	1775
Pediavit (750 IU vitamin A, 30 mg vitamin C, and 400 units vitamin D per millilitre)	Europharm International Canada	7450
Ranitidine, 15 mg/mL	Apotex Inc	624
Sodium phosphate (4.8 mmol sodium and 4.2 mmol phosphate per millilitre)	Odan Laboratories	7480
Vitamin E (Aquasol E), 50 units/mL	Columbia Laboratories Canada	3563
Zidovudine, 10 mg/mL	ViiV Healthcare	3455
Compounded		
Atenolol, 2 mg/mL	Nahata et al.[4]	3385
Caffeine, 10 mg/mL	Eisenberg and Kang[5]	82
Dexamethasone, 1 mg/mL	Nahata et al.[4]	353
Diazoxide, 10 mg/mL*	Jackson[6]	1695
Domperidone, 1 mg/mL	Ensom et al.[7]	1850
Hydrocortisone, 1 mg/mL	The Hospital for Sick Children[8]	1850
Levetiracetam, 50 mg/mL	Ensom et al.[9]	1855
Phytonadione, 1 mg/mL†	Compounded from injection†	25
Sildenafil, 2.5 mg/mL	Allen[10]	1690
Spironolactone-hydrochlorothiazide, 5 mg/mL each	Allen and Erickson[11]	1810
Trimethoprim, 10 mg/mL	The Hospital for Sick Children[8]	3000
Ursodiol, 50 mg/mL	The Hospital for Sick Children[8]	1530

*Made with 100-mg capsules and Ora-Blend vehicle (Medisca).

†Made by dilution of 10 mg/mL injection with sterile water, as used for in-house stability testing by the original manufacturer, Sabex, in 1993.

phytonadione and dexamethasone (both of which were injectable products that are given enterally in our setting), as well as caffeine (which is specifically compounded for preterm neonates). Compounds made from injection solutions or formulated specifically for neonates may have lower osmolalities than those made with sweetened and preserved diluents; however, this supposition would need confirmation through further osmolality measurements of multiple compounded oral liquid medications.

Our results demonstrate the lack of appropriate neonatal medication formulations available from manufacturers and a lack of appropriate compounding recipes for neonates.

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Amanda Leong, BScPharm, ACPR, is with Pharmacy Services, Saskatchewan Health Authority, Regina, Saskatchewan.

Alison Gordon, BScPharm, is with Pharmacy Services, Alberta Health Services, Calgary, Alberta.

Belal Alshaikh, MD, MSc, is with the Division of Neonatology, Department of Pediatrics, University of Calgary, Calgary, Alberta.

Kamran Yusuf, MD, is with the Division of Neonatology, Department of Pediatrics, University of Calgary, Calgary, Alberta.

Deonne Dersch-Mills, BScPharm, ACPR, PharmD, is with Pharmacy Services, Alberta Health Services, Calgary, Alberta.

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Address correspondence to:
Dr Deonne Dersch-Mills
Pediatrics & Neonatology, Inpatient Pharmacy
Alberta Children's Hospital
28 Oki Drive NW
Calgary AB T3B 6A8
e-mail: deonne.dersch-mills@ahs.ca

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Cannabinoid Hyperemesis Syndrome: A Case Report and Discussion Regarding Patients with Concurrent Disorders

Stephen Lee-Cheong, Amrita Grewal, Lukas Hestvik, Reza Rafizadeh, and Christian Schütz

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INTRODUCTION

In October 2018, Canada legalized the nonmedical use of cannabis. Usage has traditionally been high in Canada, and after legalization, self-reported use increased from 14% to 18%.[1] Given this increased usage, it is important to understand the adverse effects of cannabis. Here, we focus on a less well-recognized consequence, cannabinoid hyperemesis syndrome (CHS), first described in 2004.[2] It may be seen more often in jurisdictions where cannabis is legalized; for example, from 2009 to 2011, after legalization of cannabis in the state of Colorado, presentations to emergency departments for CHS increased by almost 100%.[3]

CHS presents similarly to cyclic vomiting syndrome, with recurrent nausea and vomiting episodes interspersed with asymptomatic periods.[4] However, several features differentiate CHS from cyclic vomiting syndrome. CHS is associated with a history of chronic cannabis use, cure of the syndrome after cessation of cannabis, and delayed gastric emptying.[4] Cyclic vomiting syndrome is often associated with concurrent migraines and psychiatric conditions, as well as rapid gastric emptying.[4] The prodromal phase lasts up to several years in CHS,[4] but just minutes to hours in cyclic vomiting syndrome.[5]

The following characteristics seem to have the highest sensitivity for diagnosis of CHS: weekly cannabis use for more than 1 year, severe nausea and vomiting with abdominal pain repeating in a cyclic pattern over months, resolution of symptoms after cannabis cessation, and compulsive use of hot baths or showers to provide temporary symptom relief.[6] Normal bowel habits are cited as supportive criteria. However, abnormal bowel habits do not necessarily rule out CHS, as there are a number of recorded cases, including the patient described in this report, with both CHS and abnormal bowel habits.[7] The complications of CHS, which are due to recurrent vomiting, include fluid and electrolyte disorders, nutritional deficiencies, aspiration, pneumonitis, and esophageal wall injury.[8] Unfortunately, given that CHS is poorly recognized, patients often undergo potentially harmful procedures such as radiography, computed tomography (CT), endoscopy, and appendectomy in search of a diagnosis.[4] Here, we describe CHS by means of a clinical case and then discuss the challenges that may be encountered within the subpopulation of patients with concurrent disorders.

CASE REPORT

A 29-year-old man (height 185 cm, weight 84 kg) with a history of schizophrenia, epilepsy, major depressive disorder, cannabis use disorder, and opioid use disorder was admitted in early October 2019 to a treatment centre for concurrent disorders.* After 1 month (starting on October 30), he experienced an 8-day episode of vomiting, diarrhea, and associated nausea. He reported having had 5 hospital admissions during the first half of the year for similar presentations, stating that each of these episodes subsided spontaneously after about 5 days. He further reported about 2 episodes annually for the past 10 years.

The patient described severe cramping abdominal pain lasting throughout the day, rated as 8–10 (on a scale of 1 to 10) during the first several days and then 5–6 near the end of the 8-day period. He denied fever and associated flu-like symptoms, but had been experiencing night sweats for the past 2 months. The patient vomited 3 or 4 times per day during the 8-day episode and experienced nausea only about 15 min before vomiting. During the initial days of the episode, he experienced 3 to 5 episodes of diarrhea associated with vomiting when eating.

The family history was noncontributory for gastrointestinal disease or illness. His father had diagnoses of post-traumatic stress disorder, major depressive disorder, and schizophrenia.

Before admission to the treatment centre, the patient had been living in an apartment with a friend; he was

*The patient provided verbal informed consent for the publication of this case report.

unemployed and was receiving disability support. He was single with no dependants.

The patient denied cannabis use for the past month (i.e., since admission to the treatment centre), although this statement was inconsistent with the results of urine drug screening, which were positive for tetrahydrocannabinol (THC) on the day his symptoms started. However, 1 week earlier, the results of urine drug screening had been negative for THC, amphetamines, methamphetamine, benzodiazepines, cocaine, opiates, fentanyl, methadone, and oxycodone. He reported that his last use of opioids was 2 months prior, which was consistent with staff observations and all prior urine drug screening results; this ruled out opioid withdrawal as the cause of his symptoms. The patient had started smoking cannabis at 12 years of age and smoked heavily (3–4 g/day) around the age of 15. Previous to the onset of his symptoms, he had smoked 1 pack of cigarettes daily for the last 4 years and smoked fentanyl once per month for the last 3 years.

The patient's regular medications were suboxone 16 mg SL daily, escitalopram 20 mg PO daily, carbamazepine extended-release 600 mg PO at bedtime, paliperidone 263 mg IM q12weeks, and pantoprazole 40 mg PO at bedtime.

The patient was admitted to the internal medicine service at a separate facility 4 days after symptom onset. On admission to that facility, he was alert and oriented; the mucous membranes were slightly dry, the chest was clear to auscultation, and heart sounds were normal. Jugular venous pressure was also normal. Rectal examination results were negative for occult blood and rectal masses. The white blood cell count was 14.9 (normal range 4.0–11.0) $\times 10^9$/L with left shift, hemoglobin was 152 g/L, and the platelet count was 306×10^9/L. Blood pressure was 129/84 mm Hg, heart rate 107/min, respiratory rate 22/min, temperature 37.5 °C, and oxygen saturation by pulse oximetry 98% on room air. Electrolyte results were unremarkable.

The patient was given IV fluids, ondansetron, and dimenhydrinate, which helped to reduce the symptoms slightly. More specifically, ondansetron 4 mg SL tid PRN was given initially, and the dosage was then switched to 8 mg PO bid after slight symptom improvement. Dimenhydrinate 50 mg IM stat was given twice, which controlled vomiting episodes effectively; loperamide 2 mg PO PRN provided diarrhea control. CT of the abdomen and pelvis showed that the appendix appeared normal. He had a history of intestinal parasites at 10 years of age, and there were current self-reports of poor hand hygiene. This information prompted collection of stool samples for culture; the results were negative for all parasites and *Helicobacter pylori*. No other significant abnormality could be found, and the patient was discharged back to the treatment centre (after a 6-h stay) without full resolution of his symptoms.

Upon return to the treatment centre, ginger (20-mg tablets; 1 or 2 tablets PO q4h PRN) was trialled for several days for treatment of nausea, without effect. Acetaminophen 1000 mg PO q6h PRN for pain did not relieve the patient's stomach cramps. He achieved symptomatic relief by using a heating pad on his abdomen throughout the day and experienced about 20 min of relief by showering with hot water, which he did 3 to 12 times daily. At this point, staff in the treatment centre diagnosed CHS, on the basis of presentation and the exclusion of other diagnoses. The patient's observed "excessive" showering was related to "self-treatment" and not to any psychotic disorder or symptoms of obsessive-compulsive disorder.[2] He had full resolution of symptoms after about 10 days.

DISCUSSION

The patient described here was an inpatient at a treatment and recovery centre for patients with concurrent disorders, which provided comprehensive integrated care for severe mental health and substance use disorders. Patients at this centre often present with the complex chief concern of vague nausea and vomiting of a chronic, intermittent nature. Many of the patients are marginalized and have a detrimental "lifestyle" arising from a lack of daily structures and unhealthy nutrition.[9] As staff in the centre, we have proposed that lifestyle choices (excessive use of coffee, tobacco, and/or alcohol) may contribute to perpetuation of these symptoms and potential diagnostic delay.

For CHS, as with any medical syndrome, it is important to carefully seek out the cause of the symptoms and to conduct diagnostic screening to exclude effects of other substances, such as opioid withdrawal; adverse effects of medication abuse, such as intermittent gastroenteritis or gastroesophageal reflux disease (GERD); neurological disorders, such as migraine; or pregnancy. According to the guidelines on the management of cyclic vomiting syndrome in adults, rigorous and repetitive diagnostic testing is often required before this particular diagnosis is even included in the differential diagnosis.[10] Careful exclusion of other diagnoses is necessary, as was done here for intestinal parasites and *H. pylori*. Testing to exclude gallbladder and pancreatic abnormalities is also suggested as part of the workup.[2]

Within the field of addiction recovery, staff regularly view nausea and vomiting as consequences of problematic lifestyle choices, including excessive intake of coffee, tobacco, and/or alcohol, which may cause GERD.[11] Excessive caffeine intake is common among patients with mental health disorders, particularly schizophrenia.[12] Studies of patients with schizophrenia have reported consumption of more than 750 mg of caffeine daily.[13] Alcohol may also lead to alcoholic gastritis,[14] and poor hygiene may lead to *H. pylori* infection.[15] However, the patient described here did not drink caffeine or alcohol. These factors, which cause symptoms similar to those of CHS, may act as distractors in the development of a differential diagnosis, because they may cause symptom prolongation and overlap. For example,

the prodromal phase described by Allen and others[2] may be misinterpreted in the presence of any of these factors. Diagnosis of CHS may also be delayed by a lack of awareness about the syndrome, as has been suggested throughout the current literature.[4,7,16,17] Aside from taking the appropriate diagnostic approach, it is important that the consequences or complications of nausea and vomiting (e.g., fluid depletion, hypokalemia, and metabolic alkalosis) are identified and corrected.

There are several hypotheses for the pathophysiological mechanisms for CHS. One is the desensitization and downregulation of the CB1 cannabinoid receptors, which ordinarily have antiemetic effects (GRADE [Grading of Recommendations Assessment, Development and Evaluation] rating very low).[16] Cannabis is used as an antiemetic,[18] which has been discussed as another factor that may cause perpetuation of the syndrome.[2] At the time of symptom onset, people with CHS may increase their cannabis usage in an attempt to self-medicate, thereby inadvertently perpetuating and worsening their symptoms. Allen and others[2] found a dose-related response in their study.

High-quality evidence for pharmacologic treatment of CHS is limited.[2] The only definitive treatment identified to date is abstinence from cannabis (GRADE rating low),[16] with full resolution typically taking 7 to 10 days.[2] Benzodiazepines are the most commonly reported treatment option, followed by haloperidol and topical capsaicin[2]; first-line antiemetics have been found to be ineffective, although did have some efficacy in this case.[16] A challenging caveat is that benzodiazepines are drugs of abuse and therefore contraindicated for these patients. Tricyclic antidepressants also have some efficacy,[2] although were not given in this case because of the potential for interaction with escitalopram. Short-term relief of symptoms by means of hot showers or topical capsaicin may be due to activation of transient receptor potential vanilloid 1 ($TRPV_1$) through interaction with the endocannabinoid system.[16,17]

With the recent legalization of cannabis in Canada, it is important that conditions like CHS receive appropriate attention. This can be achieved, as suggested by previous authors,[4,7,16] by increasing the amount of research on the subject that is conducted and published, as we have done here. In addition, it would be prudent for the government to increase awareness of cannabis complications through warnings on packages, as is done for tobacco products. Given that hospital admissions due to CHS are likely to increase, we propose building CHS screening protocols or tools to be used at the hospital level for patients who present with nausea, diarrhea, and/or stomach pain. Being more readily able to discuss cannabis use with patients may help direct physicians toward a more accurate diagnosis.

This case has highlighted the difficulty of diagnosis and treatment of CHS in a population of patients with concurrent disorders, including unnecessary exposure to potentially harmful procedures such as CT. One challenge that can arise in any population, but particularly this one, is dealing with poor reporting of the history by the patient. In this case, it was not possible to confirm the amount of cannabis that was being used, because the patient denied any use at all; this forced the team to use clinical judgment. The patient expressed much frustration with the situation, and although he admitted to being aware that cannabis was the source of his symptoms, he continued to deny any recent usage.

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Stephen Lee-Cheong, MB, BCh, BAO, is a student in the Post-Graduate Certificate in Pain Management program of the Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Alberta.

Amrita Grewal, BSc, PharmD, was, at the time of this study, a student in the PharmD program of the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia. She has since graduated from the program.

Lukas Hestvik, MN-NP(F), BSN, is with the Burnaby Centre for Mental Health and Addiction, Burnaby, British Columbia.

Reza Rafizadeh, BSPharm, ACPR, BCPP, RPh, is with The University of British Columbia and the BC Psychosis Program, Vancouver, British Columbia, and is also with the Burnaby Centre for Mental Health and Addiction, Burnaby, British Columbia.

Christian Schütz, MD, PhD, MPH, FRCPC, is with the University of British Columbia, Vancouver, British Columbia, and the Burnaby Centre for Mental Health and Addiction, Burnaby, British Columbia.

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Address correspondence to:
Dr Stephen Lee-Cheong
Noel Lee-Cheong Medical Professional Corporation
2155 Lawrence Avenue East, Unit 109
Scarborough ON M1R 5G9

e-mail: stephenleecheong@gmail.com

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Should Hospital Admission Be Used as an Opportunity for Deprescribing in Older Adults?

THE "PRO" SIDE

Polypharmacy, defined as the use of 5 or more medications, is becoming increasingly common in older adults, internationally. For example, in a Canadian survey of experiences with primary health care, 27% of older adults reported taking 5 or more medications on a regular basis.[1] Polypharmacy is associated with medication-related adverse effects such as frailty, disability, death, and falls.[2] Deprescribing—the process of withdrawing an inappropriate medication, under the supervision of a health care professional, with the goal of managing polypharmacy and improving outcomes—may be a solution to reduce the harm associated with using multiple medications.[3] Evidence is accumulating to suggest that initiating deprescribing interventions within the hospital setting can be feasible, safe, and sustained after discharge. For patients with polypharmacy, admission to hospital can give clinicians an opportunity to reassess medications, identify the risks and harms of the current medication regimen, and initiate deprescribing of inappropriate medications, because the necessary resources, time, and specialist health care practitioners are often readily available in this setting. Hospitals also represent a somewhat "controlled" environment, where clinicians can closely monitor and reassess patients after implementing deprescribing interventions. To evaluate whether hospitalization should be used as an opportunity for deprescribing, the effectiveness of hospital-based deprescribing interventions must be analyzed.

A recent systematic review of randomized trials evaluating the impact of deprescribing interventions on older adults in hospital demonstrated that such interventions are safe, feasible, and generally effective in reducing potentially inappropriate medications.[4] Since publication of this systematic review, many other studies have provided additional evidence to support the proposition that hospitalization offers an opportunity for deprescribing in older adults.

In a single-arm interventional study, hospitalized Canadian patients aged 65 years or older, who were long-term regular users of sedative medications, received a self-directed patient education pamphlet describing the risks of prolonged use of sedatives and outlining a stepwise tapering protocol.[5] These hospitalized older adults were willing to discontinue their sedative medications, and of the 50 participants enrolled in the study, 32 (64%) had successful deprescribing of their sedative medication in hospital, with no reported episodes of acute withdrawal. Importantly, the study found no change in self-reported sleep disturbances after the hospital stay (relative to preadmission occurrences), which indicates that the intervention was feasible and safe.

In another study, conducted in Australia, McKean and others[6] investigated whether a structured approach to deprescribing was feasible and whether it reduced medication burden. A sample of 50 hospital inpatients aged 65 years or older underwent a deprescribing intervention, which included an education program targeted toward clinicians and implementation of a 5-step decision support tool for selecting eligible medications for discontinuation.[7] The intervention resulted in a significant decrease in the median number of medications per patient at discharge. At follow-up, less than 5% of ceased medications were recommenced, and this occurred among less than 10% of the patients. There were no deaths or acute presentations to hospital attributable to ceasing the medications. These findings demonstrate that a multifactorial hospital intervention can lead to safe and successful deprescribing of inappropriate medications in older adults. Similarly, a study conducted in an Australian tertiary hospital evaluated the feasibility of a pharmacist-led, physician-supported deprescribing model, in which patients 65 years or older with polypharmacy were evaluated for deprescribing by team pharmacists.[8] In that study, 60% of patients had successful deprescribing of inappropriate medications, which showed that this model of deprescribing in an acute hospital setting is feasible and that deprescribing is becoming an essential role for clinical pharmacists.[9]

A further example involved a prospective dual-arm interventional study conducted in a Canadian tertiary care hospital.[10] The study aimed to reduce the number of medications prescribed at hospital discharge following pharmacist-led, patient-specific deprescribing rounds for inpatients. The deprescribing rounds resulted in significantly more medications being deprescribed relative to the control, with a significant reduction in rates of hospital readmission and presentations to the emergency department.

There is also some evidence to suggest that not initiating deprescribing interventions in hospital may be a missed opportunity to improve medication use in older adults. In the United Kingdom, a study to quantify and describe the nature of deprescribing in a teaching hospital found limited deprescribing activity, dominated by reactive behaviour from clinicians (such as a response to an adverse clinical trigger), as opposed to proactive efforts to deprescribe inappropriate medications.[11] Similarly, in a Canadian study,[12] the rates of use and discontinuation of docusate sodium and

other laxatives by internal medicine inpatients was documented; the investigators found that docusate was frequently and inappropriately prescribed to hospital inpatients, with approximately 80% of patients continuing docusate use at the time of discharge. These results demonstrate that deprescribing interventions are needed within hospital settings to reduce inappropriate use of medications.

Overall, the growing evidence from systematic reviews and interventional studies suggests that hospitalization may be a good opportunity to initiate deprescribing interventions for older adults. Often, deprescribing needs to be actively promoted to health care practitioners and patients, with the message that it should not be considered as an isolated task, but rather forms part of a comprehensive medication management review for older adults.[13] The patient's or caregiver's goals and attitudes to their health and medications should always be considered before commencing any deprescribing interventions.

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Lisa Kouladjian O'Donnell, BMedSc(Hons), MPharm, PhD
Departments of Clinical Pharmacology and of Aged Care
Kolling Institute of Medical Research, Royal North Shore Hospital
St Leonards, New South Wales, Australia
Northern Clinical School, Faculty of Medicine and Health
The University of Sydney
Sydney, New South Wales, Australia

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THE "CON" SIDE

Two of every 3 Canadians over the age of 65 years take 5 or more prescription medications, often referred to as polypharmacy.[1] Polypharmacy can be appropriate and necessary, occurring as a result of multimorbidity combined with an extended lifespan. However, more than 30% of older Canadian adults are taking 1 or more potentially inappropriate medications (PIMs; defined as medications for which the risk outweighs the benefit).[1] Deprescribing is the process of reducing or discontinuing inappropriate medications, with the goal of reducing risk and negative outcomes in older adults.[2] Research focused on deprescribing is growing; however, the current literature is heterogeneous, involving different types of interventions, providers, and contexts, with variable efficacy.[3,4]

Several points of opportunity for deprescribing have been described in the literature.[5-7] Hospital admission, in particular, is thought to provide an ideal opportunity for deprescribing, because the patient's medication history is reviewed, clinicians are working in a collaborative environment, and patients and families are engaged in the process during the hospital stay.[3,4,8] However, there are significant challenges to deprescribing in the hospital setting that limit this opportunity.[5-7] First, hospital admission is often the result of an acute issue, making deprescribing of long-term medications less of a priority. Indeed, changes to regular medications during hospitalization could cause new symptoms or a change in condition, which could influence monitoring of recovery from the acute issue. A 2018 narrative review determined that more research was required regarding clinicians' safety concerns related to deprescribing, such as withdrawal events and re-emergence of a condition.[9]

The time needed for deprescribing of certain medications (e.g., need for tapering) and continuity of care in the context of short admissions are also of concern. Given the economic costs, as well as the known risks during a hospital stay (e.g., errors, infection, deconditioning), lengthening a hospital stay to allow for deprescribing is unlikely to be appropriate. One in-hospital study, published in 2018, showed that hospital admission is itself a risk factor for prescribing of a PIM.[10]

In addition, issues related to fragmentation of care are exacerbated in hospital. These issues include difficulties

accessing medical and/or medication history and the various specialties and clinicians involved in past and present care. Inability to access a patient's complete history limits the possibility of identifying whether a medication is inappropriate and therefore suitable for deprescribing. As well, reluctance to question what a colleague has prescribed may lead to hesitancy among clinicians to initiate the deprescribing process or review the need for a medication.[7,11]

Guidelines, along with diagnoses, test results, and symptoms, are used by clinicians to guide decision-making; they also promote a prescribing culture and subsequent polypharmacy. Typically, guidelines provide information about when to initiate a medication, but often neglect to provide information about discontinuation.[12] Although deprescribing tools and guidelines are emerging, there is as yet no consistent process for or guide to this process. Lack of confidence among prescribers, combined with an absence of reliable decision support, may lead to continuation of medications, as this may be perceived as safer than discontinuation.[11,13] As well, the effect of decision support tools requires more research. An in-hospital study of a decision support tool, published in 2019, showed a statistically significant decrease in PIMs with use of the tool; however, the effect on clinically significant outcomes was unclear.[4] Overall, the impact of in-hospital deprescribing on clinically important outcomes is unknown, because studies have not been powered to evaluate outcomes such as readmission and mortality.[3] In an already strained health care system, in-hospital activities that improve clinical outcomes should be prioritized.

Patients' preferences and goals of care also play a role in deprescribing. In a survey of older inpatients, 89% were hypothetically willing to stop 1 or more of their regular medications.[8] However, attempts to deprescribe in clinical trials have not shown the same rate of success.[14,15] In a cross-sectional study published in 2018, 39.7% of patients refused deprescribing in hospital, and none of the variables measured, including number of PIMs, predicted refusal.[15] Overall, patient characteristics and factors leading to patients' refusal of deprescribing constitute an area for further exploration. Another in-hospital study, published in 2019, highlighted the importance of patient education and engagement in the deprescribing process.[7] The ability to discuss and ascertain patient preferences to drive appropriate deprescribing may be diminished in hospital, because there is no previously established relationship between patients and their care providers. The patient's level of trust and the physician–patient relationship are likely to be hugely influential in the success of deprescribing.[8,16] Additionally, for patients experiencing an acute event or an otherwise significant point in their health care journey, it is not clear whether preferences expressed while in hospital will fluctuate or match preferences after discharge.

Transitions of care are particularly concerning and can affect the success of deprescribing.[17,18] Lack of follow-up and absence of assumption of responsibility for patients in whom deprescribing has been initiated, especially those without a family doctor, are issues for prescribers.[3,7] The literature shows that deprescribing efforts are often not sustained after hospital discharge, as approximately 25% of ceased medications are restarted within the following year.[19] This often occurs even if the medication was discontinued because of an adverse effect or as part of a comprehensive assessment. Problems with transfer of information and the involvement of multiple health care providers are cited as possible causes for resumption of medications; however, the reasons for re-prescription of ceased medications require further research.[19,20] Therefore, without appropriate communication channels following discharge, deprescribing during hospitalization may be futile and not a valuable use of time and resources.

Evidence exists of the barriers to deprescribing in hospital; for example, an evaluation of deprescribing in the hospital setting, published in 2018, showed that only 4% of patients had a medication deprescribed.[21] It has also been shown that deprescribing in hospital tends to be reactive, not proactive.[21] Because of these barriers, further research is required before hospitalization can be considered an "ideal" setting for deprescribing. Nonetheless, clinicians should make the most of every opportunity to increase patients' and clinicians' awareness of deprescribing. Education of patients and clinicians and initiation of discussions about deprescribing could certainly start in the hospital, as could identification of PIMs that should be reviewed by the primary care team. Communication and continuity during transitions of care are key, and discussions should be continued after discharge, with patients, families, and health care providers becoming informed and engaged in shared decision-making.

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Marci E Dearing, BSc(Pharm), PharmD, ACPR
QEII Health Sciences Centre, Nova Scotia Health Authority
Halifax, Nova Scotia

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Should Therapeutic Monitoring of Vancomycin Based on Area under the Curve Become Standard Practice for Patients with Confirmed or Suspected Methicillin-Resistant *Staphylococcus aureus* Infection? The "Pro" Side: Correction

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In the Point Counterpoint debate in the May–June 2020 issue, paragraph 4 of the "Pro" article contained some errors. Specifically, reference 11 should *not* have been cited with the opening sentence, and that sentence should have ended with the word "limited" (not "lacking"); the complete sentence should read as follows: "Data correlating attainment of the target vancomycin trough with improved clinical outcomes are limited." In the same paragraph, the fourth and fifth sentences should be replaced with the following corrected sentence: "Kullar and others[11] [*Clin Infect Dis*. 2011;52(8):975-81] found an association between trough and clinical outcomes and also found a similar result with respect to the AUC/MIC cut-off as above."

De l'autre côté du miroir

par Douglas Doucette

Alors que nous entamons les derniers mois de l'année 2020, je suppose que bon nombre d'entre nous ont souvent eu l'impression de traverser le miroir, comme dans le roman du XIX^{e} siècle de Lewis Carroll, qui raconte des voyages fantastiques et décrit des interactions avec des personnages invraisemblables et inattendus. La plupart des Canadiens n'ont jamais connu de pandémie et ne savaient vraisemblablement pas à quoi s'attendre lorsque les comptes-rendus sur la COVID-19 et sa propagation imminente à l'échelle planétaire ont commencé à circuler.

Notre vie professionnelle et personnelle a été irrémédiablement bouleversée. La pandémie a obligé les associations sans but lucratif, comme la Société canadienne des pharmaciens d'hôpitaux (SCPH), à adapter leurs activités de bureau ainsi que les programmes et les services qu'elles offraient à leurs membres. Le Conseil et les succursales de la SCPH ont réexaminé leurs priorités, mis davantage l'accent sur certaines activités et reporté ou suspendu d'autres à cause des pressions financières exacerbées par la pandémie. Le *Journal canadien de la pharmacie hospitalière* (JCPH) a été directement touché par des mesures de réduction des coûts. Afin de préserver la grande qualité du Journal et de diminuer les coûts de production, le nombre de numéros du JCPH a été réduit à quatre par an au lieu de six. De plus, le système de soumission du JCPH et son interface de publication sont en cours de migration vers un système plus efficace et plus économique qui permettra de rationaliser le flux de travail. Il offrira en outre aux lecteurs davantage de fonctionnalités.

Au cours de ces derniers mois, j'ai réfléchi aux expériences que j'ai vécues au cours de mon mandat de trois ans en tant que président de la SCPH. J'ai eu l'occasion de rencontrer des acteurs clés de Santé Canada, de l'ANORP, de l'ACEIP, de l'ACSP et d'autres, qui m'ont fait part de points de vue divers sur les enjeux auxquels font face les soins de santé et la pharmacie. En tant que président, j'ai répondu aux questions des médias et d'autres associations, comme on peut s'y attendre, mais leurs thèmes et leur calendrier n'étaient pas toujours prévisibles. Je remercie le personnel du bureau et les collègues de l'équipe présidentielle de leur soutien pendant que je me préparais à ces entrevues. Cependant, je n'ai pas pu anticiper certaines situations, comme le départ à la retraite de Myrella Roy, notre directrice générale de longue date, peu après mon élection à la présidence. Ce fut un privilège de travailler avec elle pendant une partie de mon mandat, mais j'ai dû ensuite diriger le groupe de travail chargé de trouver son successeur. En 2019, le Conseil a vécu des moments passionnants lors du choix de la nouvelle directrice générale, Jody Ciufo, et quant à moi, ce fut un privilège de l'accompagner dans sa prise de contact avec la SCPH et la pharmacie hospitalière en général. Nous avons travaillé main dans la main sur la Stratégie de développement durable pour établir notre feuille de route future en tant qu'association nationale. Nous avons également pris le temps de célébrer le 50^{e} anniversaire de notre Congrès sur la pratique professionnelle et de réfléchir sur le long chemin parcouru par notre profession, en partie grâce au leadership de la SCPH et de ses membres.

Le Plan stratégique de 2020-2023 de la SCPH sera bientôt rendu public (si ce n'est pas déjà fait). Il trace la voie à suivre pour améliorer la valeur de la Société pour ses membres ainsi que sa stabilité fiscale au moyen de priorités stratégiques bien définies. En tant que porte-parole de la pharmacie hospitalière au Canada, la SCPH a continué de faire preuve d'un solide leadership à l'égard d'enjeux clés pour la défense des intérêts dans les domaines du Programme national d'assurance-médicaments, de la déclaration obligatoire de réactions adverses aux médicaments et de l'importation aux É.-U. de médicaments canadiens. À la fin de 2020, les recommandations émanant de notre groupe de travail sur le cannabis et de celui sur les techniciens en pharmacie devraient être soumises à l'examen du Conseil pour qu'il oriente les travaux dans ces deux domaines.

Il y a trois ans, peu d'entre nous auraient pu imaginer où nous en serions en tant que Société aujourd'hui. Si nous regardons de l'autre côté du miroir et au-delà, il est peut-être encore plus difficile de prédire l'avenir à la lumière de la pandémie de COVID-19 et de l'envergure de ses effets. L'engagement et le professionnalisme que démontrent les membres des équipes de la pharmacie hospitalière tant pour conduire la riposte que pour gérer les pénuries de médicaments et les soins aux patients en ces moments difficiles illustrent combien notre profession est essentielle à la santé des Canadiens. Je suis heureux d'avoir été au service de cette société nationale solide, résolue et engagée en tant que membre de l'équipe présidentielle, et je me réjouis de voir ce que nous accomplirons au cours des années à venir.

[Traduction par l'éditeur]

Douglas Doucette, B. Sc. (Pharm.), Pharm. D., F.C.S.H.P., était au moment de la rédaction, président sortant et agent de liaison externe pour la Société canadienne des pharmaciens d'hôpitaux (SCPH). En date du 17 octobre 2020, il a terminé son mandat de trois ans en tant que membre de l'équipe présidentielle de la SCPH.

Through the Looking-Glass

Douglas Doucette

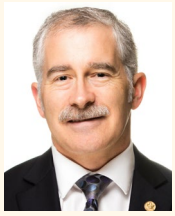
As we enter the final months of 2020, I suspect many of us have often felt this year like Alice going through the looking-glass in Lewis Carroll's 19th century fictional novel of fantastical travel and interactions with unlikely and unexpected characters. Most Canadians had not been through a pandemic and likely did not know what to expect when reports of COVID-19 and its imminent spread around the world began to circulate.

Our professional and personal lives have been irrevocably changed. The pandemic has caused nonprofit associations like the Canadian Society of Hospital Pharmacists (CSHP) to adjust office operations, member services, and programs. The CSHP Board and Branches reviewed their priorities, shifting focus onto select activities and deferring or suspending others, due to financial pressures exacerbated by the pandemic. The *Canadian Journal of Hospital Pharmacy (CJHP)* has been directly affected by recent cost-cutting measures. To maintain the high quality of the Journal and save on the cost of production, the *CJHP* has been reduced to 4 issues a year from 6. In addition, the *CJHP*'s submission system and publishing interface are being moved to a more efficient, cost-effective system that will streamline the Journal's workflow and offer readers more functionality.

These last few months, I have been reflecting on the experiences I have had during my 3-year term as a CSHP presidential officer. I had the opportunity to meet with key stakeholders in Health Canada, NAPRA, CAPSI, CPhA and more, which provided multifaceted insights into pharmacy and health care issues. As President, I responded to the media and other associations, as expected, but the topic and timing could not always be predicted. I am grateful to the office staff and fellow presidential officers for their support as I prepared for these interviews. There were circumstances I did not anticipate, however, such as the retirement of Myrella Roy, our long-serving Executive Director, shortly after I became President Elect. It was a privilege to work with Myrella for part of my term, but I was then charged with leading the task force to find her successor as CSHP's first Chief Executive Officer. It was an exciting time for the Board to select and for me to help orient the new CEO, Jody Ciufo, in 2019 to CSHP and hospital pharmacy in general. We worked together on the Strategy Towards Sustainability to chart our future as a national association. We also took time to celebrate the 50th anniversary of our Professional Practice Conference and reflect on how far our profession has come, in part, thanks to CSHP leadership and its members.

CSHP's Strategic Plan for 2020-2023 will soon (if it hasn't already) be released. It plots the path for improving member value and fiscal stability through defined, strategic priorities. As the voice of hospital pharmacy in Canada, CSHP has continued to show significant leadership on key advocacy issues in the areas of national pharmacare, mandatory reporting of serious adverse drug reactions, and the US importation of Canadian drugs. By late 2020, the recommendations from our Cannabis Task Force and Pharmacy Technician Task Force should be available for consideration by the Board to guide work on those two areas.

Looking back 3 years ago, few could have imagined where we would be as a Society today. Gazing into the looking-glass and beyond, it is perhaps even more difficult to predict the future in light of the COVID-19 pandemic and its far-ranging effects. The dedication and professionalism demonstrated by hospital pharmacy teams from leading the response to managing drug shortages and caring for patients in these challenging times has shown how essential our profession is to the health of Canadians. I am proud to have served as a presidential officer of this strong, resolute, and dedicated national society, and I am looking forward to seeing what we will accomplish in the years to come.



Douglas Doucette, BSc(Pharm), PharmD, FCSHP, was, at the time of writing, Past President and External Liaison for the Canadian Society of Hospital Pharmacists (CSHP). As of October 17, 2020, he completed his 3-year term as a presidential officer of CSHP.

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