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Vol. 75, nº 1, Hiver 2022
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Sault Ste Marie, Ontario

In this issue / Dans ce numéro :

- Cytomegalovirus Viremia in Renal Transplant Recipients
- Antimicrobial Use in an Outpatient Hemodialysis Unit
- Nocturnal Hypoglycemia Associated with Bedtime Insulin Administration
- Real-World Effectiveness and Safety of Palbociclib plus Endocrine Therapy
- Preoperative Hyperglycemia in Surgical Patients with Diabetes
- Perceptions of the Clinical Pharmacist Role
- Levetiracetam for Status Epilepticus in Adults
- Gestion des approvisionnements en médicaments pendant la pandémie de COVID-19
- When No Treatment Is the Treatment (Case Report)

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Pages 1–64

EDITORIAL / ÉDITORIAL

Why I Got My COVID Shot 3
Susan K Bowles

La raison pour laquelle je me suis fait vacciner contre la COVID-19. 4
Susan K Bowles

ORIGINAL RESEARCH / RECHERCHE ORIGINALE

Characterization of Cytomegalovirus Viremia in Renal Transplant Recipients. 6
Ishan Chaudhari, Marianna Leung, and Bita Bateni

Patterns of Antimicrobial Use in an Outpatient Hemodialysis Unit 15
Sylvia Sivarajahkumar, Miranda So, Andrew M Morris, Charmaine Lok, Chaim M Bell, and Marisa Battistella

Nocturnal Hypoglycemia Associated with Bedtime Administration of Premixed Insulin Preparations in Hospitalized Patients 21
Kelsey K Mann, Heather Neville, and John Robert Manderville

Effectiveness and Safety of Palbociclib plus Endocrine Therapy in Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer: Real-World Results. 26
Cristina Fernández-Cuerva, Juan Carlos del Rio Valencia, and Rocio Tamayo Bermejo

Risk Factors for Preoperative Hyperglycemia in Surgical Patients with Diabetes: A Case–Control Study 34
Peter Van Herk, Nathaniel Morin, Deonne Dersch-Mills, Rhonda Roedler, Beverly Ang, and Lori Olivieri

BRIEF RESEARCH REPORT / BREF RAPPORT DE RECHERCHE

Health Care Professionals' Perceptions of the Role of the Clinical Pharmacist and Expanded Pharmacist Coverage in Critical Care 41
Kristin Kaupp, Emma K Reid, Hannah Corney, Sarah Burgess, and Lauren Hutton

REVIEW / ARTICLE DE SYNTHÈSE

Levetiracetam for Status Epilepticus in Adults: A Systematic Review 46
Carly A Webb, Richard Wanbon, and Erica D Otto

INNOVATIONS IN PHARMACY PRACTICE / INNOVATIONS DANS LA PRATIQUE PHARMACEUTIQUE

Gestion des approvisionnements en médicaments pendant la pandémie de COVID-19 : expérience québécoise en établissement de santé 54
Lucie Verret, Marie-Claude Racine, Diem Vo, François Paradis, Geneviève Cayer, Cécile Lecours, Isabelle Nolet et Jean-François Bussières

CASE REPORT / OBSERVATION CLINIQUE

When No Treatment Is the Treatment: Mental Illness–Related Case Report 58
Colette Raphaël and Ofer Agid

EXECUTIVE COMMENTARY / COMMENTAIRE DE LA DIRECTION

To Go Far, Go Together 63
Zack Dumont

Si on veut aller loin, il faut partir ensemble 64
Zack Dumont

On the Front Cover / En page couverture. 14

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Why I Got My COVID Shot

Susan K Bowles

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As I write this editorial in autumn 2021, Canada has seen 1.74 million cases of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), almost 30 000 deaths, and close to 90 000 hospitalizations, bringing our health care system to the breaking point.[1]

Although the country has experienced epidemics of serious infectious diseases in the past, such as polio and smallpox, these have largely been forgotten. The development of vaccines for these diseases served as important milestones in their management, but—as with the vaccines for SARS-CoV-2—they were sometimes met with mistrust and hesitancy.[2] However, the SARS-CoV-2 vaccines have been subjected to an unprecedented campaign of dis- and misinformation, largely driven by social media.[3]

In the months since SARS-CoV-2 vaccines became available in Canada, I have had countless discussions with patients, substitute decision-makers, and colleagues who have expressed concern about the vaccines. I have tried my best to follow the principles of communicating with vaccine-hesitant individuals, a discussion of which is beyond the scope of this editorial and which are, in any case, well described elsewhere.[2,4] But on almost every occasion, I have been asked the question, "Why did you get your vaccine?"

Reflecting on the reasons for getting the SARS-CoV-2 vaccine, I realize it comes down to these two: science and a sense of professional responsibility. Results from clinical trials for the SARS-CoV-2 vaccines were impressive with regard to vaccine efficacy, though with the caveat that the findings of clinical trials do not necessarily translate to effectiveness under real-world conditions. Breakthrough infections were inevitable, but almost one year later, it is reassuring that surveillance systems have demonstrated that vaccination continues to protect against hospitalization and serious complications.[1] There is also concern about vaccine safety. To say that the SARS-CoV-2 vaccines are without side effects would be misleading, and serious adverse effects have been identified through extensive monitoring. But the risk of these adverse effects is lower than the risk of complications from the SARS-CoV-2 infection itself.[5,6] I preferred the odds in favour of vaccination.

It has been a privilege to have spent the last thirty-plus years as a self-regulated health professional, recognizing that privilege comes with responsibility. While it remains to be definitively determined whether protecting myself through vaccination reduces viral transmission to others,[7] I still have a responsibility to model health behaviours for others. If I were not vaccinated, how would that influence the vaccination decision for my patients and colleagues? What harm would that do to my community and to my workplace?

Many are drawn to a career in health care by an interest and trust in scientific methods, along with a strong sense of responsibility to apply scientific knowledge for the benefit of not only individual patients, but also the broader population. We must appreciate, however, that not all people share this trust, especially as it pertains to vaccines. Jonas Salk recognized the importance of leading by example when he injected himself and his family with the polio vaccine that he had developed. While this practice would fall well outside the ethical standards of today, the principle of leading by example remains. Can we expect others to do what we say if we aren't willing to do it ourselves?

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La raison pour laquelle je me suis fait vacciner contre la COVID-19

par Susan K Bowles

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Alors que j'écris cet éditorial à l'automne 2021, le Canada enregistre 1,74 million de cas d'infection par le syndrome respiratoire aigu sévère coronavirus 2 (SRAS-CoV-2), près de 30 000 décès et près de 90 000 hospitalisations, poussant ainsi notre système de santé jusqu'au point de rupture[1].

Bien que le pays ait connu des épidémies de maladies infectieuses graves dans le passé, telles que la polio et la variole, celles-ci ont été largement oubliées. Le développement de vaccins contre ces maladies a constitué des jalons importants dans leur contrôle, mais – comme dans le cas des vaccins contre le SRAS-CoV-2 – ils ont parfois été accueillis avec méfiance et hésitation[2]. Cependant, les vaccins contre le SRAS-CoV-2 ont été soumis à une campagne de désinformation sans précédent, largement alimentée par les médias sociaux[3].

Au cours des mois qui se sont écoulés depuis que ces vaccins sont disponibles au Canada, j'ai eu d'innombrables discussions avec des patients, des mandataires spéciaux et des collègues qui ont exprimé leur inquiétude face aux vaccins contre le SRAS-CoV-2. J'ai fait de mon mieux pour suivre les principes de communication avec les personnes hésitantes – dont la discussion dépasse le cadre de cet éditorial, et qui sont de toute façon bien décrits ailleurs[2,4]. Mais presque chaque fois, on m'a posé la question « Pourquoi vous êtes-vous fait vacciner? »

En réfléchissant aux raisons de se faire vacciner contre le SRAS-CoV-2, je me rends compte qu'elles se résument à deux éléments : la science et le sens des responsabilités professionnelles. Les résultats des essais cliniques relatifs aux vaccins contre le SRAS-CoV-2 ont été impressionnants sur le plan de l'efficacité, malgré la réserve que les résultats d'essais cliniques ne se traduisent pas nécessairement dans des conditions réelles. Les infections perthérapeutiques étaient inévitables certes, mais près d'un an plus tard, le fait que les systèmes de surveillance aient démontré que la vaccination continuait de protéger le public contre les hospitalisations et les complications graves est rassurant[1]. L'innocuité des vaccins suscite également des inquiétudes. Dire que les vaccins contre le SRAS-CoV-2 n'ont pas d'effets secondaires serait trompeur, et des effets indésirables graves ont été décelés grâce à une surveillance approfondie. Mais ce risque est inférieur à celui engendré par les complications de l'infection par le SRAS-CoV-2[5,6]. J'ai donc préféré placer mes chances en faveur de la vaccination.

Ce fut un privilège de passer les plus de trente dernières années en tant que membre d'une profession de la santé autoréglementée, mais je reconnais que ce privilège s'accompagne d'une responsabilité. Même s'il reste à déterminer avec certitude si se protéger en se faisant vacciner réduit la transmission virale[7], j'ai encore la responsabilité de donner l'exemple. Si je n'étais pas vaccinée, comment ce comportement influencerait-il la décision de mes patients et collègues de le faire (ou non)? Comment cela affecterait-il ma communauté et mon lieu de travail?

Pour de nombreuses personnes, c'est l'intérêt pour les méthodes scientifiques et la confiance en celles-ci qui les attirent vers une carrière dans les soins de santé, de concert avec un sens aigu de la responsabilité d'appliquer des connaissances scientifiques au profit non seulement des patients, mais aussi de la population au sens large. Nous devons cependant comprendre que tout le monde ne partage pas cette confiance, en particulier en ce qui a trait aux vaccins. Pour montrer l'importance de donner l'exemple, Jonas Salk s'est lui-même administré le vaccin contre la polio qu'il avait mis au point et l'a administré à sa famille. Même si cette pratique dépasse largement les normes éthiques d'aujourd'hui, le principe de prêcher par l'exemple reste ancré. Pouvons-nous attendre d'autrui de faire ce que nous disons si nous ne sommes pas disposés à le faire nous-mêmes?

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Characterization of Cytomegalovirus Viremia in Renal Transplant Recipients

Ishan Chaudhari, Marianna Leung, and Bita Bateni

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ABSTRACT

Background: Kidney transplantation, while improving outcomes for patients with end-stage renal disease, comes with a risk of potentially life-threatening infections such as infection with cytomegalovirus (CMV), a virus associated with allograft rejection, organ dysfunction, and increased mortality.

Objectives: To characterize whether the choice and dose of immunosuppressant therapy and the duration of antiviral prophylaxis after transplant are associated with the incidence of CMV viremia.

Methods: This study was a retrospective review of all kidney-only transplant recipients at the authors' centre from 2012 to 2016, with a minimum 1 year of follow-up. Patients with CMV viremia (defined as serum CMV viral load greater than 1000 IU/mL) were compared with patients who did not have viremia to investigate potential demographic and treatment-related risk factors.

Results: A total of 653 patients were included in the study, of whom 161 (25%) met the criteria for CMV viremia. In univariate analysis, patients with CMV viremia had older age (55 versus 53 years, $p = 0.038$) and lower mean body weight (75 versus 79 kg, $p = 0.015$); in addition, the CMV viremia group included larger proportions of patients with Asian descent (40% [64/161] versus 21% [104/492]) and donor-positive/recipient-negative CMV serostatus (29% [47/161] versus 14% [70/492]). With respect to immunosuppressant therapy, patients with CMV viremia more frequently received antithymocyte globulin (ATG) induction (50% [80/161] versus 28% [138/492], $p < 0.001$) and received a higher weight-based cumulative ATG dose (mean 4.5 versus 4.1 mg/kg, $p = 0.038$). The multivariate analysis retained use of ATG, cumulative dose of ATG, Asian descent, and CMV serostatus as risk factors for CMV viremia. No statistically significant differences were found for the maintenance immunosuppressant dosing or duration of antiviral prophylaxis.

Conclusions: Use of ATG for induction and higher weight-based dose of ATG were associated with an increased risk of CMV viremia. In addition, a component of race may also be involved, with patients of Asian descent being at higher risk. No differences were found in the maintenance dose of immunosuppression or the duration of antiviral prophylaxis.

Keywords: cytomegalovirus, viremia, kidney transplant recipient, antithymocyte globulin, mycophenolate mofetil, valganciclovir

RÉSUMÉ

Contexte : La transplantation rénale, bien qu'elle améliore les résultats des patients atteints d'insuffisance rénale en phase terminale, s'accompagne d'un risque d'infections potentiellement mortelles telles que l'infection par le cytomégalovirus (CMV) : un virus associé au rejet d'allogreffe, à un dysfonctionnement d'organe et à une plus grande mortalité.

Objectifs : Caractériser si le choix et la dose du traitement immunosuppresseur et la durée de la prophylaxie antivirale après la transplantation sont associés à l'incidence de virémie à CMV.

Méthodes : Cette étude était un examen rétrospectif de tous les receveurs d'une transplantation rénale uniquement mené au centre des auteurs de 2012 à 2016, avec un suivi d'au moins 1 an. Les patients atteints de virémie à CMV (définie comme une charge virale sérique CMV supérieure à 1000 UI/mL) ont été comparés à des patients sans virémie; cette comparaison avait pour but d'étudier les facteurs de risque démographiques ou liés aux traitements.

Résultats : L'étude comprenait 653 patients, dont 161 (25 %) répondaient aux critères de virémie à CMV. En analyse univariée, l'âge des patients atteints de virémie à CMV était plus élevé (55 contre 53 ans, $p = 0{,}038$) et leur poids corporel moyen était moins élevé (75 contre 79 kg, $p = 0{,}015$); en outre, le groupe des patients atteints de virémie à CMV comprenait une plus grande proportion de patients d'origine asiatique (40 % [64/161] contre 21 % [104/492]) et de statut sérologique CMV donneur positif/receveur négatif (29 % [47/161] contre 14 % [70/492]). En ce qui concerne le traitement immunosuppresseur, les patients atteints de virémie à CMV ont reçu plus fréquemment une induction de sérum anti-lymphocytaire (SAL) (50 % [80/161] contre 28 % [138/492], $p < 0{,}001$) ainsi qu'une dose cumulative de SAL plus élevée en fonction du poids (moyenne de 4,5 contre 4,1 mg/kg, $p = 0{,}038$). L'analyse multivariée a retenu l'utilisation du SAL, la dose cumulative de SAL, l'origine asiatique et le statut sérologique du CMV comme facteurs de risque de virémie à CMV. Aucune différence statistiquement significative n'a été trouvée pour la posologie d'entretien des immunosuppresseurs ou la durée de la prophylaxie antivirale.

Conclusions : L'utilisation du SAL pour l'induction et une dose plus élevée de SAL en fonction du poids étaient associées à un risque accru de virémie à CMV. De plus, une composante raciale pourrait également être impliquée – les patients d'origine asiatique étant plus à risque. Aucune différence n'a été trouvée dans la posologie d'entretien des immunosuppresseurs ou la durée de la prophylaxie antivirale.

Mots-clés : cytomégalovirus, virémie, transplanté rénal, globuline antithymocyte, sérum anti-lymphocytaire, mycophénolate mofétil, valganciclovir

INTRODUCTION

To ensure transplant success, kidney transplant recipients require profound immunosuppression, which places them at risk of serious life-threatening infections. One pathogen of concern is cytomegalovirus (CMV), a member of the herpesvirus family that is found latently in large segments of the global population.[1] In the setting of immunosuppression, reactivation of the virus may cause significant disease, potentially resulting in allograft rejection, organ dysfunction, or death.[1,2] CMV disease can be further described as CMV syndrome (infection with fever, malaise, leukopenia, and/or thrombocytopenia) or tissue-invasive CMV disease (infection resulting in organ dysfunction, such as enteritis, colitis, hepatitis, pancreatitis, pneumonitis, meningoencephalitis, and retinitis).[2]

Multiple studies have placed the incidence of CMV viremia between 20% and 30% among kidney transplant recipients.[3-5] Although the most significant risk factor for CMV viremia is the CMV serostatus of the donor and recipient (D/R), with donor-positive and recipient-negative (D+/R–) status having the highest risk, several other demographic and clinical parameters have been identified as risk factors, such as older age, deceased donor, duration of hemodialysis before transplant, and estimated glomerular filtration rate (eGFR) after transplant.[5-8]

In addition to these pre- and post-transplant risk factors, certain other post-transplant factors, such as the choice of induction and maintenance immunosuppression, have also been implicated in the incidence of CMV infections. Agents of interest have included antithymocyte globulin (ATG), tacrolimus, and mycophenolate mofetil (MMF).[5,7,8] However, there is currently a paucity of information in the literature as to whether the dose intensity of these agents is associated with CMV viremia. An example is the therapeutic regimen for MMF, which at our site is initiated and maintained at a dose of 1 g twice daily, irrespective of body weight (except in cases of intolerable adverse effects, such as neutropenia or diarrhea). There is concern that this dosing strategy may place patients with lower body weight (and thus a higher per-kilogram dose of MMF) at greater risk of immunosuppressive complications. Pharmacokinetic studies have implicated lower body weight with a higher area under the curve for mycophenolic acid.[9,10] A study conducted by Tsang and others[11] comparing MMF and azathioprine therapy in Chinese kidney transplant recipients found that among the 41 patients who received MMF, a dose of 2 g/day resulted in a significantly higher incidence of CMV infection relative to MMF doses of 1.5 and 1 g/day. However, it is unclear whether these findings warrant adopting a weight-based dosing strategy to prevent immunosuppressive complications.

For select patients with higher-risk D/R serostatus or ATG induction, a key preventive strategy is the initiation of CMV prophylaxis after transplant. At our site, this is most commonly achieved with administration of the oral antiviral agent valganciclovir. The usual duration for CMV prophylaxis ranges from as long as 6 months for cases involving D+/R– CMV serostatus to just 1–3 months for cases involving CMV-positive recipients who received ATG induction. Recipients with basiliximab induction do not receive CMV prophylaxis unless the CMV serostatus is D+/R–. Anecdotal reports indicate that CMV infections appear to be more frequent among kidney transplant recipients with shorter duration of post-transplant prophylaxis. Hence, there is also great interest in the duration of antiviral prophylaxis and its relation with the subsequent incidence of CMV viremia. Although there is evidence supporting the use of longer-duration prophylaxis (up to 200 days) for cases with D+/R– CMV serostatus,[12] there are limited data on the optimal duration of prophylaxis for cases involving other serostatus combinations.

The objective of our study was to identify post-transplant risk factors for CMV viremia. In particular, we studied the choice and dosing regimen of induction and maintenance immunosuppressants and examined whether CMV viremia was associated with a shorter duration of valganciclovir prophylaxis.

METHODS

Study Design and Data Sources

We conducted a single-centre retrospective study of kidney-only transplant recipients who underwent their surgery between January 1, 2012, and December 31, 2016, with a minimum 1 year of follow-up. To identify potential risk factors for CMV viremia, we compared patients with and without CMV viremia. CMV viremia was defined as at least 1 serum CMV viral load greater than 1000 IU/mL. This cut-off was selected to mirror our institutional definition of CMV viremia in 2012.

The study was conducted at St Paul's Hospital, in Vancouver, Canada. Data for the incidence of viremia, patient demographic characteristics, and immunosuppressant exposure were extracted from the Patient Records and Outcome Management Information System (PROMIS) electronic renal database. PROMIS is the provincial clinical information system employed by renal and transplant centres in British Columbia to coordinate patient care, record clinical data, and support research. The data included within the database reflect pre- and post-transplant care throughout a patient's lifetime once registered with the transplant program.

This study was approved by Providence Health Care Research Ethics Board, and informed consent was not required.

Data Collection

Demographic characteristics collected were age, sex, weight at time of transplant, race, CMV D/R serostatus, donor type,

cause of end-stage renal disease, number of renal transplants, dialysis requirement before transplant, dialysis vintage, panel-reactive antibody, number of human leukocyte antigen (HLA) mismatches, and results of pretransplant virological testing, such as HIV, hepatitis, and Epstein–Barr virus. Clinical outcomes extracted were eGFR 1 year after transplant, BK virus co-infection, graft failure, graft rejection, and death. For patients with CMV viremia, additional data collected were peak viral load and time to viremia.

For the analysis of induction immunosuppression, we documented use of ATG, use of basiliximab, or no induction. Patients who received both basiliximab and at least 1 dose of ATG were categorized as having received ATG induction. The cumulative weight-based dose of ATG was calculated using total ATG doses administered divided by the patient's weight at the time of transplant. Cumulative ATG dose was then compared between patients with and without viremia who received at least 1 dose of ATG.

Maintenance immunosuppression was assessed by collecting the use of tacrolimus, MMF, mycophenolic acid, and/or cyclosporine. Drug exposure data were also collected for tacrolimus and MMF, the 2 most commonly used maintenance immunosuppressants at our site. For patients receiving tacrolimus, drug exposure was defined as the average trough concentrations for the following 4 periods after the transplant: day 0 to 30, month 1 to month 3, month 4 to month 6, and month 7 to month 12. These timeframes were selected to reflect the declining therapeutic trough targets for tacrolimus after transplant. For MMF, drug exposure was defined as the average daily MMF dose per kilogram body weight (mg/kg/day) for the same periods as outlined for tacrolimus. No drug exposure data are reported for mycophenolic acid and cyclosporine because of low utilization at our site.

With respect to antiviral prophylaxis, the use and duration of valganciclovir prophylaxis were collected. Patients were deemed to have received valganciclovir for CMV prophylaxis if this drug was initiated within 5 days after the transplant date and before the first episode of CMV viremia.

Statistical Analysis

Categorical variables are reported as frequencies and percentages, with analysis by the χ^2 test. Quantitative variables are reported as means with standard deviations (SDs), with analysis by *t* test. Statistical tests were conducted at the $\alpha = 0.05$ level of significance. Multivariate analysis was conducted with logistic regression, with adjustment for statistically significant confounders identified in the univariate analysis.

RESULTS

Baseline Characteristics

A total of 653 patients received a kidney transplant at our centre during the 5-year study period. Of these, 161 (25%) met our definition of CMV viremia. As demonstrated in Table 1, those with CMV viremia were older (55 versus 53 years, $p = 0.038$) and had lower body weight (75 versus 79 kg, $p = 0.015$), with greater proportions being of Asian descent (40% versus 21%) and having CMV serostatus D+/R– (29% versus 14%) or D+/R+ (44% versus 36%). Other statistically significant differences included more deceased donors, greater prevalence of dialysis, longer duration of dialysis before transplant, and higher percentage with panel-reactive antibody in the group with CMV viremia. Although there was a greater proportion of female patients among those with CMV viremia, the difference was not statistically significant. No significant differences were observed between the 2 groups in terms of diagnosis of end-stage renal disease, number of prior transplants, number of HLA mismatches, or other aspects of pretransplant virology status.

Kidney transplant recipients with CMV viremia had lower eGFR at 1 year after transplant compared with non-viremic patients (mean 47.1 versus 56.6 mL/min/m^2, $p < 0.001$). No statistically significant differences in BK virus co-infection, graft failure, graft rejection, or death were observed (data not shown).

Immunosuppression and Duration of Valganciclovir Prophylaxis

Table 2 and Figure 1 illustrate the differences in induction regimens used. Kidney transplant recipients with CMV viremia had significantly higher use of ATG for induction (50% versus 28%) and a higher mean cumulative weight-based ATG dose (4.5 [SD 1.7] versus 4.1 [SD 1.5] mg/kg, $p = 0.038$).

Table 3 illustrates differences in maintenance immunosuppression between the groups with and without viremia. We did not observe any higher tacrolimus or MMF exposure by weight in the group with CMV viremia. On the contrary, it was the group without CMV viremia, relative to the CMV viremia group, that had a significantly higher average tacrolimus exposure from months 1 to 3 (9.3 versus 8.8 µg/L, $p < 0.001$) and a significantly higher average MMF exposure from months 4 to 6 (21.8 versus 19.8 mg/kg/day, $p = 0.009$) and from months 7 to 12 (20.1 versus 17.3 mg/kg/day, $p < 0.001$). However, the CMV viremia group did have greater use of MMF (99% versus 96%, $p = 0.046$) and cyclosporine (9% versus 5%, $p = 0.029$) than the group without CMV viremia.

In our study, antiviral prophylaxis with valganciclovir was received by 71% (115/161) of patients with CMV viremia and 42% (205/492) of those without viremia. Among those who received prophylaxis, the mean duration of treatment was similar: 93.9 days in the group with CMV viremia versus 92.2 days in the group without CMV viremia ($p = 0.86$). When further categorized according to CMV D/R serostatus, the duration of prophylaxis was longest in the D+/R– group, but no statistically significant difference was found between the groups with and without viremia (168.2 versus 188.7 days, $p = 0.14$).

TABLE 1. Baseline Characteristics

Characteristic	CMV Status; No. (%) of Participants[a]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Age (years) (mean ± SD)	52.9 ± 13.4	55.4 ± 13.4	0.038
Sex			0.053
Male	311 (63)	88 (55)	
Female	181 (37)	73 (45)	
Weight (kg) (mean ± SD)	78.9 ± 17.7	75.0 ± 17.4	0.015
Race			< 0.001
White	349 (71)	83 (52)	
Asian	104 (21)	64 (40)	
Indigenous	17 (3)	6 (4)	
Hispanic	6 (1)	3 (2)	
Black	4 (1)	4 (2)	
Other or multiracial	12 (2)	1 (1)	
D/R CMV serostatus			< 0.001
+/–	70 (14)	47 (29)	
+/+	177 (36)	71 (44)	
–/+	122 (25)	38 (24)	
–/–	110 (22)	1 (1)	
Missing	13 (3)	4 (2)	
ESRD diagnosis			0.74
Diabetes	80 (16)	26 (16)	
Hypertension	56 (11)	19 (12)	
IgA nephropathy or glomerulonephritis	105 (21)	28 (17)	
Unknown or other	251 (51)	88 (55)	
Donor type			< 0.001
Living donor	257 (52)	53 (33)	
Standard criteria donor	147 (30)	44 (27)	
Expanded criteria donor	47 (10)	33 (20)	
Donation after cardiac death	41 (8)	31 (19)	
No. of kidney transplants			0.43
1	435 (88)	146 (91)	
≥ 2	57 (12)	15 (9)	
Dialysis before transplant	379 (77)	141 (88)	0.004
Dialysis vintage[b]			0.003
< 1 year	58 (12)	14 (9)	
1–5 years	242 (49)	78 (48)	
> 5 years	79 (16)	49 (30)	
PRA percentage			0.005
Overall	258 (52)	96 (60)	
0–19	202 (41)	60 (37)	
20–80	35 (7)	18 (11)	
> 80	21 (4)	18 (11)	
HLA mismatch			0.51
0–3	185 (38)	57 (35)	
4–6	295 (60)	103 (64)	
Missing	12 (2)	1 (1)	
Virology			
HIV	1 (< 1)	1 (1)	0.42
Hepatitis B	5 (1)	4 (2)	0.16
Hepatitis C	7 (1)	1 (1)	0.41
Epstein–Barr virus	414 (84)	143 (89)	0.18

CMV = cytomegalovirus, D = donor, ESRD = end-stage renal disease, HLA = human leukocyte antigen, IgA = immunoglobulin A, PRA = panel-reactive antibody, R = recipient, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Percentages based on those who received dialysis before transplant.

TABLE 2. Induction Agents

Agent	CMV Status; No. (%) of Patients[a]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Induction agent			< 0.001
ATG	138 (28)	80 (50)	
Basiliximab	347 (71)	78 (48)	
No induction	7 (1)	3 (2)	
Cumulative ATG dose (mg/kg) (mean ± SD)	4.1 ± 1.5	4.5 ± 1.7	0.038

ATG = antithymocyte globulin, SD = standard deviation.
[a]Except where indicated otherwise.

Characterization of Patients with CMV Viremia

A breakdown of the patients with CMV viremia by serostatus is presented in Table 4. Induction agents were similar for cases with D+/R– and D+/R+ serostatus, with D–/R+ patients more likely to receive ATG and less likely to be treated with basiliximab. Kidney transplant recipients within the high-risk serostatus group (D+/R–) received prophylaxis with valganciclovir for a longer duration, in accordance with American Society of Transplantation guidelines[2] (mean 168.2, 40.9, and 45.5 days for cases with D+/R–, D+/R+, and D–/R+ serostatus, respectively; $p < 0.001$). On average, these patients also had a significantly higher peak viral load than the moderate-risk (D+/R+) and low-risk (D–/R+) groups (66 243, 14 476, and 9031 IU/mL; $p = 0.001$). Although longer prophylaxis appeared to delay the occurrence of viremia from the time of transplant, the time to viremia after discontinuation of prophylaxis was similar for the high- and low-risk groups but shorter for the moderate-risk group.

Multivariate Analysis

The proportion of patients with ATG use was significantly higher among kidney transplant recipients with CMV viremia than among those without CMV viremia (OR 2.53, 95% confidence interval [CI] 1.79–3.73, $p < 0.001$). As described in Table 5, this result remained significant after adjustment for other potential confounders, specifically age, race, weight at transplant, donor type, CMV D/R serostatus, and duration of valganciclovir prophylaxis (OR 2.41, 95% CI 1.52–3.83, $p < 0.001$).

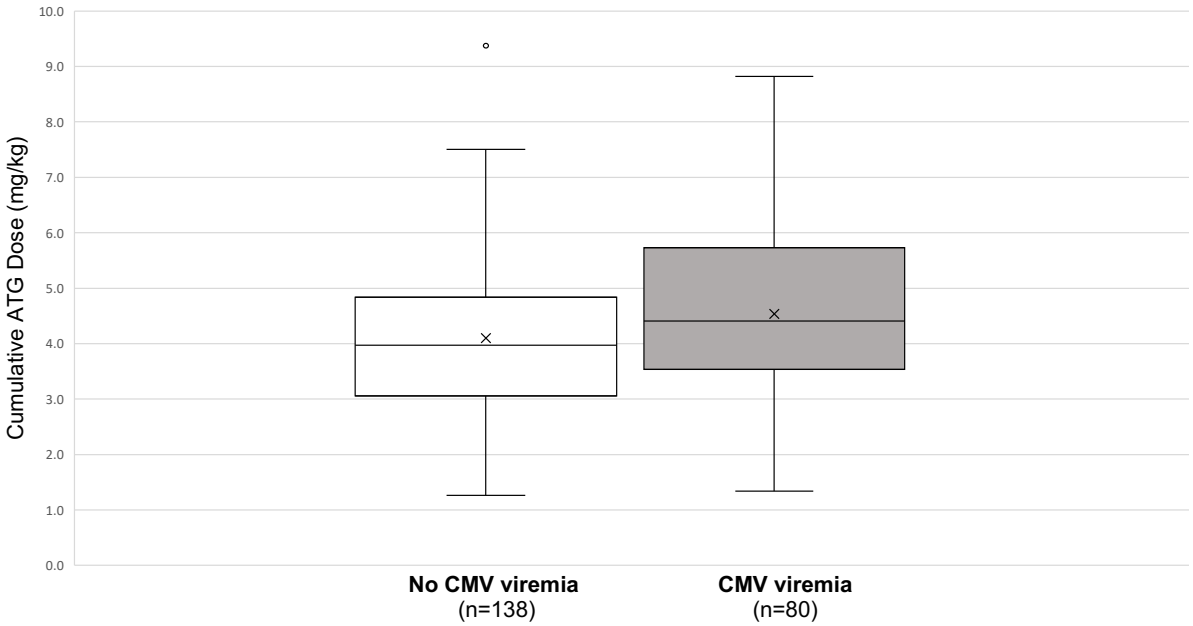

FIGURE 1. Box plot of cumulative dose of antithymocyte globulin (ATG). The horizontal line within each box denotes the median value, and the box extends vertically from the 25th percentile (bottom edge) to the 75th percentile (top edge) of values. The area of the box denotes the middle 50% of values. The whiskers denote lower and upper adjacent values (within 1.5 interquartile range of the first and third quartiles, respectively). The letter "x" denotes the mean value for each group, and the letter "o" denotes an outlier value for the group without cytomegalovirus (CMV) viremia, beyond the range of adjacent values.

TABLE 3. Maintenance Regimens

Medication[a]	CMV Status; Mean ± SD[b]		*p* Value
	No CMV (*n* = 492)	CMV (*n* = 161)	
Tacrolimus			
No. (%) of patients	479 (97)	153 (95)	0.15
Mean trough concentration (μg/L)			
Day 1–30	8.9 ± 2.3	8.6 ± 2.5	0.11
Month 1–3	9.3 ± 1.4	8.8 ± 1.4	< 0.001
Month 4–6	7.7 ± 1.4	7.6 ± 1.4	0.48
Month 7–12	6.6 ± 1.3	6.6 ± 1.2	0.69
Cyclosporine, no. (%) of patients	23 (5)	15 (9)	0.029
Mycophenolate mofetil			
No. (%) of patients	474 (96)	160 (99)	0.046
Mean dose (mg/kg/day)			
Day 1–30	25.4 ± 6.3	26.1 ± 6.6	0.20
Month 1–3	25.0 ± 6.4	24.6 ± 7.5	0.62
Month 4–6	21.8 ± 7.2	19.8 ± 8.2	0.009
Month 7–12	20.1 ± 7.1	17.3 ± 7.9	< 0.001
Mycophenolic acid, no. (%) of patients	37 (8)	11 (7)	0.77

[a]Periods for drug exposure refer to time after transplant. Drug exposure data were collected only for the maintenance immunosuppressants most commonly used at the study hospital (i.e., tacrolimus, mycophenolate mofetil).
[b]Except where indicated otherwise.

TABLE 4. Characterization of Patients with CMV Viremia

Parameter	D/R Serostatus; No. (%) of Patients[a]			*p* Value
	D+/R– (*n* = 47)	D+/R+ (*n* = 71)	D–/R+ (*n* = 38)	
Induction				0.10
ATG	19 (40)	33 (46)	26 (68)	
Basiliximab	27 (57)	37 (52)	11 (29)	
None	1 (2)	1 (1)	1 (3)	
Valganciclovir prophylaxis				< 0.001
Yes	47 (100)	38 (54)	28 (74)	
No	0 (0)	33 (46)	10 (26)	
Duration (days) (mean ± SD)	168.2 ± 77.11	40.9 ± 24.51	45.5 ± 38.20	< 0.001
Time to viremia (days) (mean ± SD)				
From transplant	278.5 ± 156.42	103.3 ± 92.34	156.3 ± 308.31	< 0.001
From end of prophylaxis	116.8 ± 47.00	60.8 ± 94.12	109.0 ± 308.78	0.36
Peak viral load (IU/mL) (mean ± SD)	66 243 ± 142 891	14 476 ± 33 501	9031 ± 15 328	0.001

ATG = antithymocyte globulin, D = donor, R = recipient, SD = standard deviation.
[a]Except where indicated otherwise.

Similarly, the cumulative ATG dose remained significantly higher in the group with CMV viremia relative to the group without CMV viremia after adjustment for the same confounders (OR 1.21, $p < 0.001$; data not shown).

DISCUSSION

We examined data for a cohort of 653 kidney transplant recipients to identify demographic and treatment-related risk factors for CMV viremia at our centre. Approximately 25% of our cohort was defined as having CMV viremia, consistent with the incidence reported in previous studies.[3-5] With respect to demographic characteristics, the univariate analysis showed that older age, Asian descent, and lower body weight were more prominent in the group with CMV viremia, although only Asian descent remained significant in the multivariate analysis (OR 2.04, 95% CI 1.25 to 3.34, $p = 0.04$). Female sex was also more represented

TABLE 5. Results of Multivariate Analysis[a]

Parameter	Adjusted OR[b] (95% CI)		*p* Value
ATG use	2.41	(1.52–3.83)	< 0.001
Age at transplant (years)	1.01	(1.00–1.03)	0.12
Weight at transplant (kg)	1.00	(0.98–1.01)	0.42
Race			0.02
Asian versus white	2.04	(1.25–3.34)	0.04
Other versus white	1.40	(0.66–2.95)	0.95
D/R serostatus			< 0.001
D+/R+ versus D−/R−	29.91	(4.02–222.47)	0.02
D+/R− versus D−/R−	87.46	(9.75–784.37)	< 0.001
D−/R+ versus D−/R−	18.57	(2.45–141.02)	0.48
Donor type (living donor versus other)	0.63	(0.41–0.99)	0.04
Valganciclovir duration		–	0.74

ATG = antithymocyte globulin, CI = confidence interval, CMV = cytomegalovirus, D = donor, OR = odds ratio, R = recipient.
[a]For kidney transplant recipients with CMV viremia, relative to those without CMV viremia.
[b]Adjusted for age, race, weight at transplant, donor type, CMV D/R serostatus, and duration of valganciclovir prophylaxis.

in the group with CMV viremia, but this variable did not reach statistical significance. It has been hypothesized that Asian patients, who on average have lower body weight, may be at increased risk of immunosuppressive complications,[10] with other studies having implicated race and sex as potential risk factors for reduced clearance of MMF.[13,14] Small studies involving Chinese patients have been able to use lower doses of MMF (1 and 1.5 g/day) while maintaining efficacy of treatment.[11,15] Tsang and others[11] found a higher incidence of CMV infection among patients receiving 2 g/day relative to those receiving 1.5 or 1 g/day of MMF, although this finding was limited by small sample size and an unclear definition of CMV. Even though our study did not show a relationship between weight-based dosing of MMF (in mg/kg) and incidence of CMV viremia, MMF dose reduction (particularly in Asian patients) may be a promising treatment modality warranting further investigation through prospective studies.

With respect to immunosuppression, the use of ATG for induction was higher among kidney transplant recipients with CMV viremia, even after adjustment for confounding factors. Our multivariate analysis also maintained the observed higher cumulative weight-based ATG dosing in the CMV group. This relationship between ATG use and CMV viremia has been documented previously.[5,16-19] Potential mechanisms include release of tumour necrosis factor-α, depletion of T-helper cells, and inversion of the CD4/CD8 ratio after administration of ATG.[16] While induction therapy is given for only a few days after transplant, one study found that ATG had a half-life of approximately 30 days.[20] Beyond this, immunosuppressive effects can persist even after ATG has cleared, with Servais and others[21] finding compromised recovery of T-cell counts up to 1 year after induction.

Nevertheless, the applicability of this finding is somewhat limited, as the study outcome (CMV viremia) is not the final clinical end point of interest. We did not collect data for the incidence of symptomatic CMV disease, such as CMV colitis or pneumonitis, because of inconsistent documentation of clinical complications in our database. Most cases of low-grade CMV viremia are asymptomatic and, if recognized early, resolve with appropriate antiviral therapy. Results from 2 small prospective studies that assessed both CMV viremia and symptomatic CMV disease demonstrated no increased risk of CMV when induction was coupled with appropriate antiviral prophylaxis.[22,23] Although our study suggested that ATG use appeared to increase the incidence of CMV viremia, it is difficult to advocate for alteration in ATG prescribing, despite our findings, given that the risk of transplant rejection far outweighs the potential benefit of mitigating a treatable viremia. However, close surveillance should be in place for patients who have received higher doses of ATG, and for patients who become unwell, there should be a low index of suspicion for CMV disease.

No differences in the dosing of maintenance immunosuppression (with tacrolimus or MMF) were identified in our study. Our initial design was intended to mimic the gradual decrease in maintenance dosing of immunosuppression seen in clinical practice. However, drug exposure was ultimately treated as a discrete variable encompassing an average over a period of time. A study design with drug exposure as a continuous variable over time might have yielded a clearer correlation. It is unclear why the group without viremia had higher average exposure to maintenance immunosuppression (with MMF and tacrolimus) in the later months. This could have been the result of confounding, as the patients with viremia were older and more

frail, and dose reductions might have been needed because of non–CMV-related adverse reactions. Alternatively, CMV infection itself or administration of valganciclovir can result in neutropenia, which would then necessitate a reduction in MMF dosage in patients with CMV. These reasons may explain why drug exposures were lower during later time intervals in the group with CMV viremia relative to those without CMV viremia.

This study also confirmed the well-documented increase in CMV risk in accordance with pretransplant D/R serostatus. Of the highest-risk group (D+/R–) in this cohort, approximately 40% developed viremia; similarly, 30% of those with CMV D+/R+ serostatus developed viremia.

We did not observe any difference in the duration of antiviral prophylaxis between the groups with and without CMV viremia. As referenced earlier, Humar and others[12] found that extended valganciclovir prophylaxis (to 200 days) in CMV D+/R– patients resulted in reduced CMV viremia and infection at 12 months relative to shorter duration of prophylaxis (for 100 days). In our study, D+/R– patients (with or without CMV viremia) received appropriate prolonged courses of valganciclovir. The other 2 risk groups (D–/R+ and D+/R+) received shorter durations of antiviral prophylaxis. However, while not statistically significant, there appeared to be a shorter duration of prophylaxis in the D+/R+ group with viremia compared to the D+/R+ group without viremia, and a reduced time to the first occurrence of viremia after finishing prophylaxis compared with the other 2 risk groups. While our overall sample size was quite large, there may have been insufficient patients for analysis once categorized by serostatus. Ultimately, a randomized prospective study would be needed to more adequately assess this issue.

This study had several other limitations. The retrospective nature of the study introduced significant potential for confounding. For instance, we observed higher panel-reactive antibody percentage and HLA mismatch in the CMV viremia group. It is unclear if these factors intrinsically increase the likelihood of CMV viremia or most likely are a product of the subsequent use of ATG. Given that all of our data were retrospectively collected from an electronic database, there is a significant risk that gaps in charting may have skewed our results. Fortunately, our data consisted largely of objective numeric data, so there is limited concern about detection bias due to lack of standardization.

CONCLUSION

This study demonstrated that patients with CMV viremia tended to be older, to have lower body weight, and to be of Asian descent. D+/R– and D+/R+ serostatus were also more strongly associated with CMV viremia. The use and higher dosing of ATG also increased the risk of CMV even when we accounted for confounding variables. There was no difference in tacrolimus trough concentrations or weight-based MMF dosing between patients with and without CMV viremia. Finally, no difference in duration of prophylactic valganciclovir was observed.

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ON THE FRONT COVER

Trees Blanketed in Snow, Sault Ste Marie, Ontario

This photograph was taken by Mary Michelina Davies using an Apple iPhone. Mary was enjoying a sunny day while cross-country skiing near her home in Sault Ste Marie when she stopped to capture this image. She works at the Sault Area Hospital on a casual basis, having retired from full-time work in September 2017. Mary has 34 years of service to the hospital and 45 years of pharmacy practice. In her spare time, she likes going for walks, exercising with her fitness club via Zoom, and reading history and fiction. She occasionally travels to London, Ontario with her husband to visit their daughter, son-in-law, and 4 young grandchildren. They keep in touch with their grandchildren using WhatsApp when not in London. This summer, Mary and her husband travelled to the east coast with their daughter and family. They visited New Brunswick, Prince Edward Island, and Nova Scotia. During the winter, Mary enjoys watching Soo Greyhounds hockey games with her husband.

The *CJHP* would be pleased to consider photographs featuring Canadian scenery taken by CSHP members for use on the front cover of the Journal. Winter-themed photographs are especially needed, so get your cameras out! If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to publications@cshp.ca.

Patterns of Antimicrobial Use in an Outpatient Hemodialysis Unit

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ABSTRACT

Background: Patients receiving hemodialysis (HD) are at high risk of infections, including those caused by multidrug-resistant organisms. Given that antimicrobial exposure is a major risk factor for the emergence of these resistant organisms, minimizing inappropriate use is imperative. To optimize use, it is important to understand patterns of antimicrobial prescribing in this setting.

Objectives: To measure antimicrobial use and to describe prescribing patterns among patients receiving outpatient HD.

Methods: A retrospective observational case series study was performed in an outpatient HD unit from February to April 2017. Adults for whom at least 1 antimicrobial was prescribed were included. The primary outcome was total antimicrobial days of therapy (DOT) per 1000 patient-days. Secondary outcomes were the characteristics of the antimicrobial prescriptions, in terms of antimicrobial class, indication, purpose, route, and prescriber group.

Results: Antimicrobials were prescribed for 53 (16%) of the 330 patients treated in the HD unit during the study period; the total number of prescriptions was 75. Antimicrobial use was 27.5 DOTs/1000 patient-days. Fluoroquinolones were the most frequently prescribed type of antimicrobial (n = 17, 23%), whereas the second most frequently prescribed were first-generation cephalosporins (n = 16, 21%). The most common indication was skin or soft-tissue infection (n = 14, 19%), followed by bloodstream infection (n = 13, 17%). Of the 75 antimicrobials, 48 (64%) were prescribed for empiric therapy, 19 (25%) for targeted therapy, and 8 (11%) for prophylaxis. Two-thirds of the antimicrobials prescribed (n = 50, 67%) were oral medications, and most (n = 72, 96%) were ordered by hospital prescribers.

Conclusions: Antimicrobial use was common in this study setting, with 1 in 6 HD patients receiving this type of medication. The findings of this study create opportunities to standardize antimicrobial prescribing at the local level for common infections that occur in patients receiving outpatient HD.

Keywords: antimicrobials, hemodialysis, infectious diseases, prescribing patterns

RÉSUMÉ

Contexte : Les patients sous hémodialyse (HD) présentent un risque élevé d'infections, y compris celles provoquées par des organismes multirésistants. Étant donné que l'exposition aux antimicrobiens est un facteur de risque majeur pour l'émergence de ces organismes résistants, il est impératif de minimiser l'utilisation inappropriée. Pour optimiser l'utilisation, il importe de comprendre les tendances de prescription d'antimicrobiens dans ce contexte.

Objectifs : Mesurer l'utilisation des antimicrobiens et décrire les schémas de prescription chez les patients recevant une HD ambulatoire.

Méthodes : Une étude rétrospective de séries de cas a été réalisée dans une unité d'hémodialyse pour patients externes de février à avril 2017. Les adultes à qui au moins 1 antimicrobien avait été prescrit ont été inclus dans l'étude. Le paramètre d'évaluation principal était le nombre total de jours de traitement antimicrobien (JTA) pour 1000 jours-patients. Les paramètres secondaires étaient les caractéristiques des prescriptions d'antimicrobiens, en termes de classe d'antimicrobiens, d'indication, d'objectif, de voie d'administration et de groupe de prescripteurs.

Résultats : Des antimicrobiens ont été prescrits à 53 (16 %) des 330 patients traités dans l'unité d'HD au cours de la période d'étude, pour un nombre total de prescriptions de 75. L'utilisation d'antimicrobiens était de 27,5 JTA/1000 jours-patients. Les fluoroquinolones étaient le type d'antimicrobien le plus fréquemment prescrit (n = 17, 23 %) et les céphalosporines de première génération (n = 16, 21 %) étaient le deuxième type. Une infection de la peau ou des tissus mous (n = 14, 19 %) était l'indication la plus courante, suivie d'une infection du sang (n = 13, 17 %). Sur les 75 antimicrobiens, 48 (64 %) ont été prescrits pour un traitement empirique, 19 (25 %) pour un traitement ciblé et 8 (11 %) pour une prophylaxie. Les deux tiers des antimicrobiens prescrits (n = 50, 67 %) étaient des médicaments oraux, et la plupart (n = 72, 96 %) ont été prescrits par des prescripteurs hospitaliers.

Conclusions : L'utilisation d'antimicrobiens était courante dans le cadre de cette étude, où 1 patient sous HD sur 6 recevait ce type de médicament. Les résultats de cette étude créent des opportunités de normaliser la prescription d'antimicrobiens au niveau local pour les infections courantes qui surviennent chez les patients recevant une HD ambulatoire.

Mots-clés : antimicrobiens, hémodialyse, maladies infectieuses, schémas de prescription

INTRODUCTION

In Canada, infection is the second leading reason, after cardiovascular disease, for admission to hospital among patients receiving long-term dialysis.[1] Patients undergoing hemodialysis (HD) are at risk of infectious complications, including those caused by multidrug-resistant organisms.[2] Risk factors for infection in patients receiving HD include dialysis-mediated immune dysfunction, frequent health care visits, and repetitive vascular access procedures, which create a portal of entry for microorganisms.[2]

The outpatient HD unit is a high-risk setting for the acquisition of multidrug-resistant organisms because of extensive antimicrobial use in this setting.[3] The increased risk represents a significant source of morbidity, potential mortality, and cost in the care of patients receiving HD.[3,4] Minimizing exposure to unnecessary antimicrobials through multifaceted antimicrobial stewardship interventions is crucial for curtailing the emergence and acquisition of multidrug-resistant organisms in this population.[5] Furthermore, unnecessary use of antimicrobials may be associated with various adverse drug events, including allergic reactions, end-organ toxic effects, and infection with *Clostridioides difficile* (formerly known as *Clostridium difficile*).[6] Hence, it is imperative to implement antimicrobial stewardship interventions in the HD unit to facilitate appropriate prescribing of antimicrobials, while minimizing harm to patients.

Implementation of antimicrobial stewardship programs in outpatient HD facilities may substantially reduce infections caused by multidrug-resistant organisms and *C. difficile*, as well as infection-related deaths and total costs, as demonstrated by D'Agata and others[7] using a health economic model. The model estimated that unnecessary antimicrobial use in the outpatient HD setting could be reduced by 20% over a 1-year period by implementing antimicrobial stewardship programs. This reduction was associated with benefits that included the prevention of 2182 infections caused by multidrug-resistant organisms and *C. difficile* (4.8% reduction), 629 fewer infection-related deaths (4.6% reduction), and cost savings of US$106 893 517 (5.0% reduction) per year in the United States.[7] Developing an effective antimicrobial stewardship program in an HD unit requires a comprehensive understanding of the antimicrobial prescribing practices that need improvement and an assessment of the prevalence of antimicrobial use in this population.[5] However, there are limited data pertaining to antimicrobial use among patients receiving HD on an outpatient basis. Previous studies have focused on prescribing of IV antimicrobials, and only 1 study described both oral and IV antimicrobials prescribed by community and hospital prescribers in the HD population.[4,8,9] Understanding both oral and IV antimicrobial use is essential, because most HD patients are managed in the outpatient setting.

We aimed to understand the overall burden of oral and IV antimicrobial use in an outpatient HD population. The primary objective of the study was to measure antimicrobial use, and the secondary objective was to describe antimicrobial prescribing patterns.

METHODS

Study Design and Setting

This study was a retrospective observational case series study conducted between February 1 and April 30, 2017, at an academic centre located in Toronto, Ontario. The study (ID: 16-6388) was approved by the academic centre's Research Ethics Board.

The study was conducted in the hospital's outpatient HD unit, which had a roster of 330 patients during the study period.

Study Population

The study population consisted of patients 18 years of age or older who were receiving HD at the study unit, for whom at least 1 oral or IV antimicrobial was prescribed by a hospital or community prescriber. Patients who were admitted to hospital were censored from the study during the period of their hospitalization.

Outcomes

The primary outcome was antimicrobial use, which was measured in terms of total antimicrobial days of therapy (DOT) per 1000 patient-days. Total DOT per 1000 patient-days is defined as the sum of days during which any amount of a specific antimicrobial agent is administered or dispensed to a particular patient (numerator), divided by a standardized denominator (e.g. patient-days).[10,11] Patient-days were counted as the period for which a patient was registered with the HD unit, including the days on which the patient received HD and the intervening non-HD days. The metric of DOT per 1000 patient-days was chosen as the primary outcome because it is currently the most accurate and preferred measure of antimicrobial use and is used by the US Centers for Disease Control and Prevention and the National Healthcare Safety Network (formerly the Nosocomial Infection Surveillance System).[12] Total DOT standardized to 1000 patient-days allows for comparison both within an institution and between institutions of different sizes.[12]

The secondary outcomes were the characteristics of the antimicrobial prescriptions, in terms of antimicrobial class, indication, purpose of therapy, route of administration, and prescriber group.

Data Collection

The following data sources were used: the infection database maintained by the HD unit, electronic health records, and medical charts. Eligible patients were identified using the

infection database. For all patients included in the study, baseline demographic data were collected from health records and medical charts. The standard of practice in the HD unit is to record antimicrobial prescriptions in a database when a pharmacist determines, while taking a medication history, that an antimicrobial has been prescribed for the patient. Data characterizing the use of antimicrobials were collected retrospectively from this database by a single investigator (S.S.).

For each patient for whom an antimicrobial was prescribed, information regarding the documented or suspected infection and details of the prescription, including drug, dose, route, frequency, duration of therapy, and prescriber group (i.e., community or hospital), was extracted from the data sources. In addition, if available, results of microbiology and culture and susceptibility testing were collected, as reported by the microbiology laboratory.

Definitions and Classifications of Infections and Antimicrobial Prescribing

The DOT was calculated by summing the total number of treatment days for individual antimicrobials.[13] For example, if a patient had prescriptions for 2 antimicrobials for 10 days, the DOT would be 20.[13] The DOT for IV antimicrobials administered in the HD unit was determined as the period from date of initiation to date of discontinuation, as recorded in the medical chart. For a course of oral antimicrobial prescribed in the community setting, the DOT was the number of days to complete the prescribed quantity, under the assumption that patients were taking the antimicrobial as prescribed. For patients who started an antimicrobial regimen in an inpatient hospital setting, doses administered in hospital were excluded. The DOT for these patients was calculated from the date on which the antimicrobial was commenced in the outpatient setting (upon hospital discharge) to the end date of therapy indicated in the patient's medical records.

An antimicrobial prescription was defined as any course of a systemic antibacterial, antifungal, or antiviral agent prescribed by a community or hospital prescriber, administered or taken through the oral or IV route. Community prescribers did not have to be affiliated with the academic centre and might have included the patient's family physician, a walk-in clinic prescriber, or a community nurse practitioner. Hospital prescribers might have included nephrologists or nurse practitioners practising in the outpatient HD unit. Each antimicrobial prescribed was considered to represent an individual antimicrobial prescription even if it was prescribed in combination with 1 or more other antimicrobials for the same indication. If the route of the antimicrobial was altered during the treatment course (e.g., switch from IV to oral), it was classified as a new antimicrobial prescription.

The purpose of therapy was categorized as empiric, targeted, or prophylactic. Empiric therapy was defined as antimicrobial treatment of a suspected or documented infection before the identification or susceptibility of the causative pathogen became available.[14] Targeted therapy was defined as antimicrobial treatment based on culture and susceptibility data.[13] Antimicrobial prophylaxis was defined as administration of 1 or more antimicrobials in the absence of a known infection, to prevent development of infection in a patient with known risk factors.[15] Prophylaxis was further categorized as preprocedural (e.g., before a dental procedure), postprocedural (e.g., after total knee replacement surgery), or other.

Infections were categorized as skin and soft-tissue infection, bloodstream infection, respiratory tract infection, urinary tract infection, bone and joint infection, *C. difficile* infection, and *Helicobacter pylori* infection. The documented indication was recorded as per the indication stated in the medical records, irrespective of the clinical definition of the infection. Prescribers were not contacted during the study to verify collected data.

Data Analysis

The data were analyzed using descriptive statistics for all variables. Means with standard deviations and medians with interquartile ranges (IQRs), as well as counts and proportions, were calculated for baseline parameters and relevant end points as appropriate.

RESULTS

Of the 330 patients in the HD unit, 53 (16%) met the inclusion criteria, with 1 or more antimicrobial prescriptions. Men accounted for 28 (53%) of the study patients, and the mean age was 61 (SD 15) years (Table 1). The median HD vintage was 31 (IQR 10–94) months, with most patients having received HD for longer than 2 years. Hypertension (41/53, 77%) and diabetes (31/53, 58%) were the most prevalent chronic comorbidities in the study population. Diabetes was the most common primary indication for HD, and about half of the patients (26/53, 49%) had a central line as the HD vascular access type.

Antimicrobial Use

A total of 76 antimicrobial prescriptions were identified, with 1 prescription excluded because of incomplete information (indication for therapy was missing). The total DOT for the 75 eligible prescriptions, calculated by summing the DOT for each individual prescription, was 817. The total follow-up time was 29 700 patient-days. The primary outcome, the overall rate of antimicrobial use, was therefore 27.5 DOT/1000 patient-days.

Antimicrobial Prescribing Patterns

The most common indications for antimicrobial therapy were skin and soft-tissue infections, closely followed by

bloodstream infections (including those related to vascular access) and respiratory tract infections (Table 2). Only 1 (2%) of the 53 patients had multiple concurrent infections, whereas 8 (15%) had multiple non-concurrent infections during the study period. Nine patients (17%) had prescriptions for more than 1 antimicrobial (concurrent) for the same indication.

Fluoroquinolones, specifically ciprofloxacin and moxifloxacin, were the most frequently prescribed antimicrobials, accounting for 17 (23%) of the 75 prescriptions, whereas the second most frequently prescribed were first-generation cephalosporins, specifically cefazolin and cephalexin (16/75, 21%). Antimicrobials by type and route of administration are shown in Figure 1.

TABLE 1. Patient Characteristics

Variable	No. (%) of Patients[a] (*n* = 53)
Age (years) (mean ± SD)	61 ± 15
Sex, male	28 (53)
Primary indication for hemodialysis	
Diabetes mellitus	25 (47)
Hypertension	9 (17)
Glomerulonephritis	6 (11)
Polycystic kidney disease	4 (8)
Other	17 (32)
Time on hemodialysis (months) (median and IQR)	31 (10–94)
Hemodialysis access type at time of antimicrobial therapy	
Central line	26 (49)
AV fistula	16 (30)
AV graft	9 (17)
Comorbidities	
Hypertension	41 (77)
Diabetes mellitus	31 (58)
Cardiovascular disease	23 (43)
Self-reported antimicrobial allergy	
Penicillin	5 (9)
Sulfa	4 (8)
Cephalosporin	2 (4)

AV = arteriovenous, IQR = interquartile range, SD = standard deviation.
[a]Except where indicated otherwise.

TABLE 2. Indications for Antimicrobial Therapy

Indication[a]	No. of Cases
Documented or suspected infection	
Skin and soft-tissue	14
Bloodstream	
Without concurrent infective endocarditis	12
With infective endocarditis	1
Respiratory tract	11
Urinary tract	9
Bone and joint	3
Clostridioides difficile	3
Helicobacter pylori	3
Prophylaxis	
Preprocedural	4
Postprocedural	1
Other[b]	3

[a]For which at least 1 antimicrobial was prescribed.
[b]"Other" includes prophylaxis for bone and joint infection, skin and soft-tissue infection, or bloodstream infection.

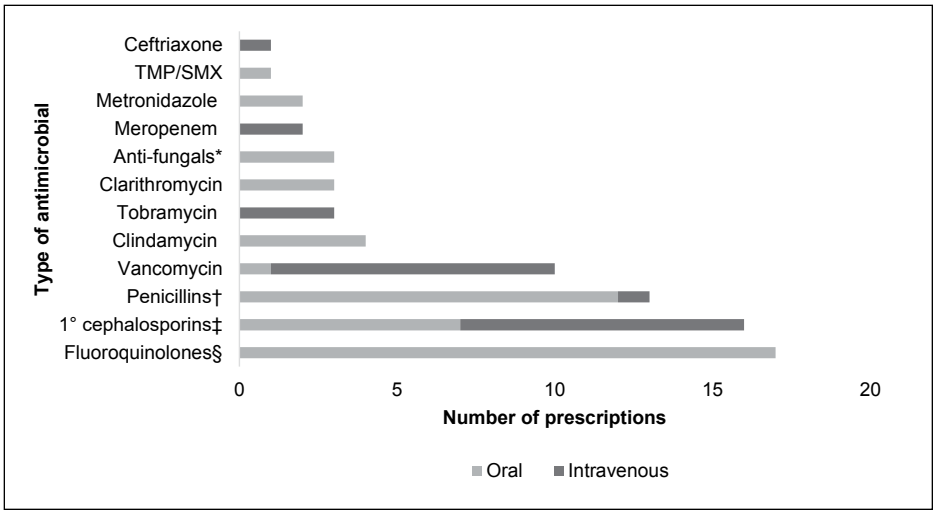

FIGURE 1. Type of antimicrobial and route of administration for 75 prescriptions. TMP/SMX = trimethoprim–sulfamethoxazole, 1° = first-generation. *Antifungals received were fluconazole and nystatin. †Penicillins received were amoxicillin, ampicillin, and amoxicillin–clavulanic acid (penicillin–β-lactamase inhibitor combination). ‡First-generation cephalosporins received were cefazolin and cephalexin. §Fluoroquinolones received were ciprofloxacin and moxifloxacin.

Two-thirds (50/75) of the antimicrobials prescribed were for oral administration, whereas the rest were for IV administration. The route of administration was altered during the treatment course for 2 of the 75 prescriptions. The oral antimicrobials most commonly prescribed were fluoroquinolones and penicillins, whereas the most commonly prescribed IV antimicrobials were cefazolin and vancomycin (Figure 1). Overall, 72 (96%) of the 75 antimicrobials were ordered by hospital prescribers.

Forty-eight (64%) of the 75 antimicrobials prescribed were for empiric therapy, with respiratory tract infections (13/48) and skin and soft-tissue infections (13/48) being the most common empirically treated infections. Nineteen (25%) of the antimicrobial prescriptions were for targeted therapy, and 8 (11%) were for prophylaxis.

DISCUSSION

The current study quantified antimicrobial use in an outpatient HD unit and characterized antimicrobial prescribing patterns. Antimicrobial use was common, with 1 of every 6 HD patients receiving antimicrobials during the 3-month study period.

To date, very few studies have explored antimicrobial use in patients receiving HD. Snyder and others[4] addressed IV antimicrobial use in 2 outpatient dialysis units in the United States. These authors concluded that IV antimicrobial use was extensive, with 1 of every 3 HD patients receiving antimicrobials during the 12-month prospective study period. A prospective observational study across 4 community and 2 in-hospital HD units in Australia assessed prescribing patterns for both oral and IV antimicrobials.[9] In the 6-month study period, Hui and others[9] found that 55% of participants received antimicrobials, and a total of 235 antibiotic regimens were prescribed (110 oral and 125 IV). Our study evaluated antimicrobial use over a shorter (3-month) period, and both the proportion of patients with antimicrobial prescriptions (16%) and the total number of regimens (75) were lower.

In the current study, the rate of antimicrobial use was 27.5 DOTs/1000 patient-days. Other studies have reported rates of 32.9 doses/100-patient months[4] and 69.1 antibiotic regimens/100-patient months.[9] The study design and antimicrobial use metric for the current study were different from those of the earlier studies,[4,9] which prevents direct comparisons of antimicrobial use rates. To our knowledge, there is no standardized method of quantifying antimicrobial use in an HD population, which may be the reason for variation in the metric used across studies.[16] Nonetheless, obtaining a baseline antimicrobial use rate is necessary to help us in evaluating the effectiveness of future antimicrobial stewardship interventions implemented in the study unit.

Fluoroquinolones were the most frequently prescribed class of antimicrobials, despite their recognized adverse effects, such as risk of *C. difficile* infections, peripheral neuropathy, QTc prolongation, hypoglycemia, and increased risk of tendonitis and tendon rupture.[17] In contrast to the current findings, Snyder and others[4] found that vancomycin was the most commonly prescribed antimicrobial, followed by cefazolin and third- or fourth-generation cephalosporins. Our results also differed from those of Hui and others,[9] who found amoxicillin–clavulanic acid and cephalexin as the most common oral antimicrobials prescribed, and vancomycin, piperacillin–tazobactam, cefazolin, and ceftriaxone as the most common IV antimicrobials. The lower use of vancomycin in our study may have been due to the low incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in our outpatient HD unit. The emergency department at our academic centre has reported an MRSA rate from blood isolates of 1%.[18]

Similar to the findings of our study, Hui and others[9] found that the top 3 most common infections were respiratory tract infections (24%), skin and soft-tissue infections (17%), and bloodstream infections (12%). In the current study, the majority of antimicrobials prescribed were for empiric therapy (64%), which is to be expected, given that antimicrobial use in the outpatient setting is often empiric in nature.[19] The use of empiric therapy is a widely recognized problem because of a lack of timely diagnostic tools in the outpatient setting.[19] In addition, for many of the infections treated in this study, such as uncomplicated skin and soft-tissue infections, microbiological testing is not the most useful tool for diagnosis.[20] These results highlight the need for more research to further explore the use and appropriateness of antimicrobials to treat these predominant infections in this population.

Most of the antimicrobials were prescribed by nephrologists in the HD unit, indicating that despite the unit focusing on an outpatient population, hospital prescribers remain the primary prescribers for antimicrobials in this setting. This implies that if antimicrobial stewardship interventions are implemented in the HD unit in the future, they may have a better chance of affecting the behaviour of nephrologist prescribers than that of external prescribers.

Our study had several strengths. To our knowledge, it is the first to evaluate the quantity of and prescribing patterns for antimicrobials prescribed to patients receiving outpatient HD in Canada, with evaluation of both IV and oral routes of administration. Existing literature on antimicrobial use in the outpatient HD population is limited to studies from the United States and Australia. The results of this study contribute valuable Canadian data to the diversity of the literature. Moreover, the findings of this study provide insight into which antimicrobial stewardship strategies have the potential to affect prescribing patterns. For example, syndrome-specific interventions focusing on the most common indications, such as skin and soft-tissue infections, bloodstream infections, and

respiratory tract infections, are possible opportunities to collaborate with prescribers to improve empiric selection of antimicrobial regimens.[21]

Several limitations of this study warrant discussion. First, the quality of the data collected was dependent on the quality and quantity of existing documentation. Although nearly all antimicrobials prescribed by prescribers practising in the HD unit are documented within the unit, capture of oral antimicrobials prescribed by community prescribers may have been unreliable. We addressed this limitation by exhausting all sources of data available. Second, the generalizability of our results was limited because of the single-centre design, and therefore the findings may not be applicable to other dialysis units. Third, the study period was short, which may not have allowed us to capture the seasonality of infectious diseases. A study of longer duration is warranted to gain a better understanding of antimicrobial exposure in the HD outpatient population. Finally, this study merely characterized antimicrobial use at a given point of time and did not assess the appropriateness of antimicrobial therapy. Assessing the quality of prescriptions by evaluating concordance with clinical guidelines would strengthen the results.

CONCLUSION

This study provides important information that can be used in developing antimicrobial stewardship interventions to standardize antimicrobial prescribing at the local level for common infections in outpatients receiving HD.

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Nocturnal Hypoglycemia Associated with Bedtime Administration of Premixed Insulin Preparations in Hospitalized Patients

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ABSTRACT

Background: Patients with diabetes mellitus for whom premixed insulin preparations (PMIPs) are ordered in the hospital setting may be at risk of hypoglycemia if the PMIP is incorrectly administered at bedtime (instead of suppertime).

Objectives: The primary objective was to determine, retrospectively, the incidence of bedtime administration of PMIPs at a tertiary teaching hospital. The secondary objective was to investigate whether bedtime administration of PMIPs led to an increase in nocturnal hypoglycemia.

Methods: Inpatient PMIP orders for the period April 1, 2013, to March 31, 2017, were extracted from the pharmacy information system of the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia. Two hundred randomly selected inpatient admissions were audited, and instances of PMIP administration after 2000 (8 PM) were recorded. Data from an additional random sample of inpatient admissions, from January 1, 2016, to December 31, 2017, were reviewed to determine whether bedtime administration of PMIPs was associated with increased incidence of nocturnal hypoglycemia, relative to suppertime administration.

Results: In the randomly selected sample of 200 inpatient admissions, a PMIP was administered at bedtime at least once during 47 admissions (24%). In the additional sample of 123 inpatient admissions during which a PMIP had been administered, the mean nocturnal hypoglycemia rate was 4.15% for suppertime administration and 14.85% for bedtime administration ($p = 0.13$).

Conclusions: For a substantial proportion of patients, PMIPs were inappropriately ordered and administered at bedtime in this hospital setting and may have been associated with nocturnal hypoglycemic events. Recommendations to reduce this practice include ongoing education and a review of preprinted order sets.

Keywords: insulin, premixed medications, hypoglycemia, hospital

RÉSUMÉ

Contexte : Les patients atteints de diabète sucré pour lesquels des préparations d'insuline prémélangées (PIPM) sont commandées en milieu hospitalier peuvent présenter un risque d'hypoglycémie si elles sont administrées à tort au coucher (au lieu de l'heure du souper).

Objectifs : L'objectif principal visait à déterminer, rétrospectivement, l'incidence de l'administration des PIPM au coucher dans un hôpital d'enseignement tertiaire. L'objectif secondaire visait quant à lui à déterminer si l'administration au coucher entraînait (ou non) une augmentation de l'hypoglycémie nocturne.

Méthodes : Les données relatives aux commandes de PIPM pour les patients hospitalisés pendant la période du 1er avril 2013 au 31 mars 2017 ont été extraites du système d'information pharmaceutique du QEII Health Sciences Centre à Halifax (N.-É.). Deux cents admissions de patients hospitalisés sélectionnées au hasard ont été vérifiées et les cas d'administration des PIPM après 2000 (20 h) ont été enregistrés. Les données d'un échantillon aléatoire supplémentaire d'admissions de patients hospitalisés du 1er janvier 2016 au 31 décembre 2017 ont été examinées afin de déterminer si l'administration au coucher des PIPM était associée à une plus grande incidence d'hypoglycémie nocturne, par rapport à l'administration au souper.

Résultats : Dans l'échantillon sélectionné au hasard de 200 admissions de patients hospitalisés, une PIPM a été administrée au coucher au moins une fois au cours de 47 admissions (24 %). Dans l'échantillon supplémentaire de 123 admissions de patients hospitalisés au cours desquelles une PIPM avait été administrée, le taux moyen d'hypoglycémie nocturne était de 4,15 % pour l'administration au souper et se montait à 14,85 % pour l'administration au coucher ($p = 0,13$).

Conclusions : Pour une proportion considérable de patients, la PIPM a été prescrite de manière inappropriée et administrée au coucher dans ce milieu hospitalier et peut avoir été associée à des événements hypoglycémiques nocturnes. Les recommandations visant à réduire cette pratique comprennent une formation continue et un examen des ensembles de commandes préimprimés.

Mots-clés : insuline, médicaments prémélangés, hypoglycémie, hôpital

INTRODUCTION

In 2015, the estimated prevalence of diabetes in Canada was 9.3% of the general population.[1] It is relatively common for persons with diabetes to be admitted to hospital,[1] and people with diabetes are more likely to require hospital admission and to have longer lengths of stay than those without this condition.[1] All patients with type 1 diabetes and more than one-quarter of those with type 2 diabetes use insulin to manage their hyperglycemia.[2] Several insulin preparations are available in Canada, including prandial insulins, basal insulins, and premixed insulin preparations (PMIPs) (Table 1).[3] The PMIPs are designed to simplify therapy by providing both basal and prandial insulin in a set ratio in a single injection. Because they contain prandial insulin, PMIPs are designed to be administered before meals.

For any patient with diabetes, the hospital environment may present unique challenges in attaining glycemic targets (Table 2).[4] Occasionally, patients who administer PMIPs at home are admitted to hospital, with continuation of their home insulin regimen. Health care providers in the hospital setting may be less familiar with the role of PMIPs and their place in therapy (relative to their knowledge of prandial and basal insulins), which could lead to an increased risk of hypoglycemia. The primary objective of our study was to determine the incidence of bedtime administration of PMIPs in the hospital setting, and the secondary objective was to examine whether bedtime administration was associated with an increased risk of nocturnal hypoglycemia.

TABLE 1. Premixed Insulin Preparations Available in Canada[3]

Product	Manufacturer
Humalog Mix 25	Eli Lilly Canada Inc
Humalog Mix 50	Eli Lilly Canada Inc
Humulin 30/70	Eli Lilly Canada Inc
Novolin ge 30/70	Novo Nordisk Canada Inc
Novolin ge 40/60	Novo Nordisk Canada Inc
Novolin ge 50/50	Novo Nordisk Canada Inc
NovoMix 30	Novo Nordisk Canada Inc

METHODS

Study Setting

This retrospective study took place in the Queen Elizabeth II Health Sciences Centre (QEII HSC) of the Nova Scotia Health Authority, in Halifax, Nova Scotia. The QEII HSC is a 950-bed tertiary academic centre that provides acute care services to Nova Scotians and specialized services to Atlantic Canadians (https://www.nshealth.ca/about-us). Consistent with institutional policy regarding quality assurance projects, research ethics board approval was not required.

Data Collection

Data were collected for 2 cohorts of interest.

Regarding the primary objective of establishing the incidence of bedtime administration of PMIPs in an inpatient setting, all inpatient insulin orders for the period April 1, 2013, to March 31, 2017, were extracted from the pharmacy information system of the QEII HSC. Single-ingredient insulin orders were excluded. The first chronological PMIP order for each patient was included. Two hundred PMIP order–associated inpatient admissions were randomly selected and audited, and instances of PMIP administration at bedtime (i.e., after 2000 [8 PM]) were recorded.

Regarding the secondary objective of investigating the association of bedtime administration of PMIPs with hypoglycemic events, PMIP orders between January 1, 2016, and December 31, 2017 (a period of 24 months) were extracted from the pharmacy information system of the QEII HSC for retrospective chart review. PMIP-associated inpatient admissions were excluded if the length of stay was less than 48 hours, if the patient received fewer than 2 administrations of a PMIP, or if overnight blood glucose readings

TABLE 2. Potential Issues Complicating In-Hospital Management of Hyperglycemia[4]

Issue	Effect on Glycemic Control
Variable oral intake	Poor oral intake may predispose the patient to hypoglycemia
Hyperalimentation	Continuous enteral or parenteral nutrition may obviate need for regularly scheduled prandial insulin
Exercise	Lack of exercise may impair glucose utilization
Medications	Vasopressors and corticosteroids may cause hyperglycemia; conversely, hypoglycemia may occur if these agents are abruptly discontinued
Acute illness	Acute illness may be associated with hyperglycemia
Unmasking of non-adherence to home medications	Forced adherence to medications not consistently taken at home can result in hypoglycemia
Unmasking of non-adherence to home dietary restrictions	Forced adherence to dietary restrictions can result in hypoglycemia

(between 2200 and 0900) were not documented. PMIP administration was categorized as "suppertime" if before or at 1800 or as "bedtime" if after 1800. Nocturnal hypoglycemia was defined as a point-of-care blood glucose reading of less than 4 mmol/L between 2200 and 0900. Rates were calculated as instances of nocturnal hypoglycemia divided by total administrations of insulin per admission, multiplied by 100.

Statistical Analysis

Descriptive analyses were performed. The association between bedtime administration of PMIP and hypoglycemic events was analyzed with the Mann-Whitney test, using SPSS software, version 25 (IBM Corporation).

RESULTS

A total of 39 854 insulin orders were extracted from the pharmacy information system, of which 2501 (6%) were for PMIPs (Figure 1). In the randomly selected sample of 200 inpatient admissions, there were 47 admissions (24%) in which at least 1 injection of PMIP was administered at bedtime (Figure 2).

In addition, 619 insulin mixture orders were extracted from the pharmacy information system for the period January 1, 2016, to December 31, 2017. After application of the exclusion criteria, there were 123 unique inpatient admissions (Figure 3). For these patients, a total of 1007 individual administrations of PMIP were recorded, of which 86% (n = 866) were given at suppertime. The mean nocturnal hypoglycemia rate was 4.15% for suppertime administration and 14.85% for bedtime administration (p = 0.13) (Table 3).

DISCUSSION

In a random sample of 200 hospital admissions for patients with a prescription for PMIPs, at least one inappropriate bedtime administration of a PMIP occurred during 24% of inpatient admissions. Furthermore, when compared with suppertime administration, bedtime administration of PMIPs resulted in more than 3 times the rate of hypoglycemia, although this result did not reach statistical significance. Despite the lack of statistical significance, these results should encourage health care institutions to carefully review policies and procedures pertaining to the use of these products. Since these preparations are designed to

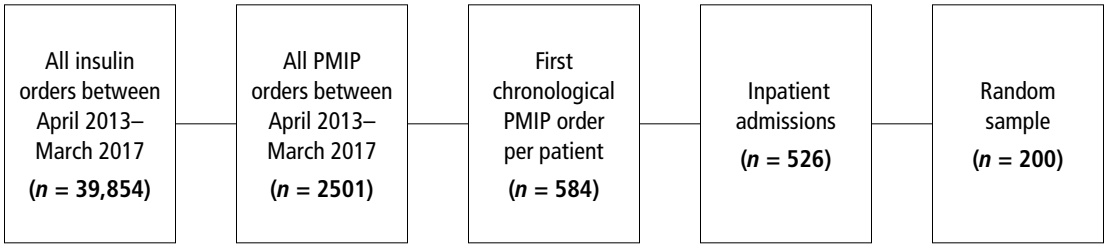

FIGURE 1. Selection of insulin orders used to establish the rate of ordering and administration of premixed insulin preparations (PMIPs) at bedtime (primary objective).

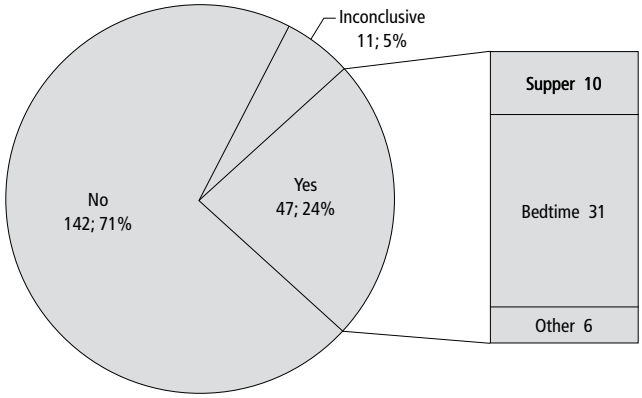

FIGURE 2. Proportion of admissions with at least 1 bedtime administration of a premixed insulin preparation (PMIP): No = no bedtime administration of PMIP; Yes = bedtime administration of PMIP; Inconclusive = time of administration could not be determined from available records. For the 47 admissions in which such a preparation was administered at bedtime ("Yes"), the intended (ordered) administration schedule (suppertime, bedtime, or other) is also shown.

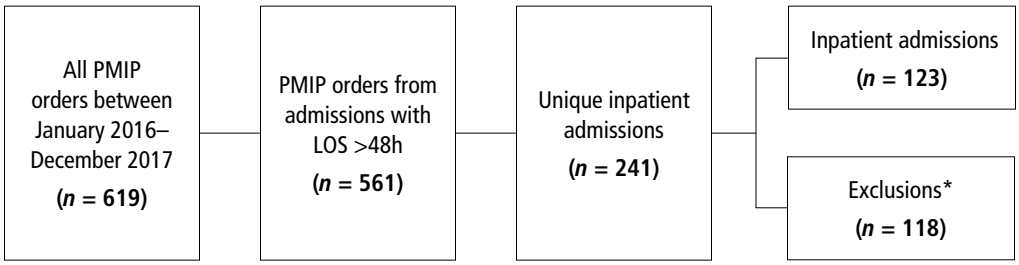

FIGURE 3. Selection of inpatient admissions for retrospective chart review to determine the incidence of nocturnal hypoglycemia (secondary objective). *Reasons for exclusions at final step of selection process: duration of therapy (with premixed insulin preparation [PMIP]) less than 48 hours (n = 39), records for second and subsequent admissions for the same patient (n = 32), PMIP administration at both suppertime and bedtime (n = 27), administration at other times (n = 17), documentation missing (n = 3). LOS = length of stay.

TABLE 3. Recorded Episodes of Hypoglycemia after Suppertime or Bedtime Administration of Premixed Insulin Preparations

	Time of Administration; Number or Mean ± SD		
Variable	**Suppertime**	**Bedtime**	***p* Value**
No. of inpatient admissions	102	21	–
No. of insulin administrations	866	141	–
Mean no. of insulin administrations per admission (pooled)	8.49 ± 7.80	6.71 ± 5.69	–
No. of hypoglycemic events	35	17	–
Mean no. of hypoglycemic events per admission (pooled)	0.34 ± 0.76	0.81 ± 1.40	
Mean nocturnal hypoglycemia rate per admission[a]	4.15% ± 10.95%	14.85% ± 26.02%	0.13

[a]The rate of nocturnal hypoglycemia for each administration time (suppertime or bedtime) was calculated as the number of instances of nocturnal hypoglycemia divided by the total number of insulin administrations at that administration time, multiplied by 100.

be given preprandially, any instances of hypoglycemia associated with improper administration at bedtime should be regarded as avoidable adverse events.

This study had some limitations. The data were collected retrospectively, and we were limited to what was documented in the health record and in the point-of-care insulin records. It was also unknown whether the patient was eating a large meal with bedtime insulin administration, which would justify a prandial dose of insulin, although this scenario is unlikely.

Blood glucose is not routinely tested during the night, and it is possible that nocturnal hypoglycemic events occurred but were not recognized and/or recorded. Individual target blood glucose levels vary depending on clinical and patient factors; therefore, for some patients, the threshold for defining hypoglycemia might have been higher than the study threshold of 4 mmol/L. If so, hypoglycemia rates may have been under-reported in our study. Finally, insulin orders may be a continuation of the patient's home administration schedule whereby, in rare circumstances, patients are admitted to hospital claiming "good" blood glucose control with bedtime injection of a PMIP.

In response to the results of this study, the QEII HSC preprinted order set for subcutaneous insulin now bears the warning "Do not give pre-mixed insulin at bedtime." We have also updated QEII HSC's "Insulin Products Available in Canada" information sheet to read, under the premixed insulin section, "Should not be given at bedtime in the hospital setting." During the study, we found several instances in which the physician's order sheet specified that the product was to be given "AM and PM", "BID", or "PM"; it is evident that any such insulin order is ambiguous as to when the second dose is to be given, and in this situation the timing should be clarified with the prescriber.

It is possible that many clinicians are not familiar with PMIPs; one Canadian insulin manufacturer estimated that total sales of PMIPs accounted for less than 14% of total insulin sales over a 3-month period in 2018.* In review articles, it is often emphasized that bedtime administration of

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NPH (neutral protamine Hagedorn) insulin may result in less nocturnal hypoglycemia than suppertime administration[5]; as such, clinicians may automatically be inclined to think that bedtime administration is preferable to suppertime administration for most insulin products.

We recognize that patients may claim to have been injecting PMIPs at bedtime at home, before their admission, without any apparent ill effects. However, it is likely that such patients were experiencing suboptimal control, and they should be made aware that this type of administration, in the absence of a large bedtime meal, could lead to hypoglycemia and should be avoided.

CONCLUSION

PMIPs were inappropriately administered at bedtime to inpatients at the QEII HSC, with a corresponding incidence of nocturnal hypoglycemia 3 times that of suppertime administration. We encourage other health care institutions to review their current practices regarding PMIP administration.

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Effectiveness and Safety of Palbociclib plus Endocrine Therapy in Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer: Real-World Results

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ABSTRACT

Background: Real-world data are critical to demonstrate the reproducibility of evidence and the external generalizability of randomized clinical trials. Palbociclib is an oral small-molecule inhibitor of cyclin-dependent kinases 4/6 that has been shown to improve progression-free survival when combined with letrozole or fulvestrant in phase 3 clinical trials.

Objective: To evaluate real-world outcomes in patients with metastatic breast cancer who received palbociclib in combination with endocrine therapy in routine clinical practice.

Methods: In this retrospective observational multicentre study, data were evaluated for all women with metastatic breast cancer who were treated with palbociclib from April 2017 to September 2019. Treatment response was assessed through progression-free survival according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

Results: Fifty-three patients were included in the study, with median age 57 years (range 31–87 years). For all patients treated with palbociclib, median progression-free survival by the end of the study period was 14.4 months (95% confidence interval [CI] 6.2–22.2 months). Twenty-three women who received palbociclib as a first-line treatment did not experience progression-free survival; for these patients, the median treatment duration was 12.1 months (95% CI 1.4–28.0 months). For the 23 patients who received palbociclib as second-line therapy for metastatic breast cancer, median progression-free survival was 13.3 months (95% CI 4.1–22.4 months). Among the 7 women who received palbociclib as third-line therapy, median progression-free survival was 6.0 months (95% CI 0.9–11.1 months). The most common adverse events were hematologic, with grade 3 or 4 neutropenia occurring in 20 (38%) of the 53 patients.

Conclusions: This study provides data from a real-world setting that match the results of previous studies in terms of effectiveness (i.e., progression-free survival) when palbociclib plus endocrine therapy was used as second- or third-line treatment. Palbociclib had appropriate tolerability and a profile of easily manageable adverse effects, with none of the patients suspending their treatment because of toxic effects.

Keywords: metastatic breast cancer, palbociclib, cyclin-dependent kinase inhibitor, letrozole, fulvestrant

RÉSUMÉ

Contexte : Les données du monde réel sont essentielles pour démontrer la reproductibilité des éléments probants et la « généralisabilité » externe des essais cliniques randomisés. Il a été démontré qu'en association avec le létrozole ou le fulvestrant dans les essais cliniques de phase 3, le palbociclib (un inhibiteur oral à petite molécule des kinases dépendantes des cyclines 4/6) améliorait la survie sans progression.

Objectif : Évaluer les résultats réels des patientes atteintes d'un cancer du sein métastatique qui ont reçu du palbociclib en association avec un traitement endocrinien dans le cadre d'une pratique clinique de routine.

Méthodes : Dans cette étude observationnelle rétrospective multicentrique, les données ont été évaluées pour toutes les femmes atteintes d'un cancer du sein métastatique et qui ont été traitées avec du palbociclib d'avril 2017 à septembre 2019. La réponse au traitement a été évaluée par la survie sans progression au moyen des critères RECIST d'évaluation de la réponse des tumeurs solides, version 1.1.

Résultats : Cinquante-trois patientes (âge médian : 57 ans; extrêmes 31-87 ans) ont été incluses dans l'étude. Pour toutes les patientes traitées avec le palbociclib, la survie moyenne sans progression à la fin de la période d'étude était de 14,4 mois (intervalle de confiance à 95 % [IC] 6,2-22,2 mois). Vingt-trois femmes ayant reçu du palbociclib en guise de traitement de première ligne n'ont pas connu de survie sans progression; pour ces patientes, la durée moyenne du traitement était de 12,1 mois (IC à 95 % 1,4-28 mois). Pour les 23 patientes ayant reçu le palbociclib en guise de traitement de deuxième ligne pour le cancer du sein métastatique, la survie moyenne sans progression était de 13,3 mois (IC à 95 % 4,1-22,4 mois). Parmi les 7 femmes ayant reçu le palbociclib en guise de traitement de troisième ligne, la survie moyenne sans progression était de 6,0 mois (IC à 95 % 0,9-11,1 mois). Les effets indésirables les plus fréquents étaient d'ordre hématologique, avec une neutropénie de grade 3 ou 4 survenant chez 20 (38 %) des 53 patientes.

Conclusions : Cette étude fournit des données provenant d'un contexte réel. Elles correspondent aux résultats d'études précédentes en termes d'efficacité (c'est-à-dire « survie sans progression ») lorsque le palbociclib, associé à un traitement endocrinien, était utilisé comme traitement de deuxième ou de troisième ligne. Le seuil de tolérance du palbociclib est approprié et son profil d'effets indésirables est facilement gérable : aucune des patientes n'a en effet suspendu son traitement en raison d'effets toxiques.

Mots-clés : cancer du sein métastatique, palbociclib, inhibiteur des kinases dépendantes des cyclines, létrozole, fulvestrant

INTRODUCTION

Breast cancer subtyping has emerged as an important strategy, providing information about prognosis and guidance in optimal treatment.[1] Breast cancer that is positive for hormone receptor (HR-positive) and negative for human epidermal growth factor receptor 2 (HER2-negative) is the most common breast cancer subtype, and for many years, endocrine therapy has been the standard treatment in women with this subtype. However, most patients have primary resistance or eventually develop secondary resistance to endocrine therapy.[2] Ideal selection of hormonal therapy is essential to overcome endocrine resistance, but new approaches are needed.[2]

Therapeutic management of HR-positive, HER2-negative metastatic breast cancer has progressed substantially with the approval of cyclin-dependent kinase (CDK) inhibitors.[3] Dysregulation in the cyclin D–CDK–retinoblastoma pathway is usually present in this type of breast cancer and is involved in resistance to endocrine monotherapy, making CDK 4/6 a highly relevant target.[3]

Palbociclib was the first CDK 4/6 inhibitor with demonstrated efficacy when combined with endocrine therapy for HR-positive, HER2-negative metastatic breast cancer in either treatment-naive or previously treated patients.[4-6] The introduction of CDK inhibitors has changed the treatment paradigm for HR-positive, HER2-negative metastatic breast cancer, leading to progression-free survival of about 24 months among treated patients in clinical trials.[7,8]

According to the toxicity profile of palbociclib, the most common grade 3 or 4 adverse events (affecting ≥ 2% of patients) are neutropenia, leukopenia, anemia, fatigue, and infections.[3,7]

Given that CDK inhibitors have been approved only recently, knowledge about the real-world experiences of women outside the context of clinical trials is needed to assess the effectiveness, toxicity profile, and tolerability of these drugs. This knowledge will in turn allow more suitable and efficient treatment interventions.

The purpose of this study was to assess the specific settings in which palbociclib combined with endocrine therapy has been prescribed in our hospitals for the treatment of HR-positive, HER2-negative metastatic breast cancer and to evaluate the real-world effectiveness of this treatment (measured in terms of progression-free survival). Our secondary objective was to review the occurrence of adverse events and changes in dosing patterns required to manage such events in the study population.

METHODS

In this observational retrospective multicentre study, we evaluated data for all women with metastatic breast cancer who were treated with palbociclib. The study population consisted of women at least 18 years of age with a diagnosis of HR-positive, HER2-negative metastatic breast cancer who received palbociclib treatment in 1 of 3 hospitals from January 2017 to September 2019, administered according to the Summary of Product Characteristic (3 weeks of treatment followed by 1 week off treatment). In addition, all of the patients received continuous treatment with 2.5 mg of letrozole per day or 500 mg of fulvestrant monthly or 25 mg of exemestane daily or 20 mg of tamoxifen administered orally. The patients were followed until April 2020. For each patient, the treatment duration was defined from the time the first dose was administered until the objective observation of disease progression (according to the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), the development of unacceptable toxic effects, or the patient's decision not to continue with the treatment.

An Excel database (Microsoft Corporation) was used to document the following study variables for each patient:

- Demographic variables: patient's sex and age when the treatment began
- Clinical variables: new diagnosis of metastatic disease or relapse, visceral or nonvisceral disease, Eastern Cooperative Oncology Group (ECOG) score at the start of therapy (measured on a 5-point scale, with 0 indicating no symptoms and higher numbers indicating greater disability),[9] hormone receptor status, and menopausal status
- Pharmacotherapeutic variables: receipt of previous courses of chemotherapy for prior metastatic disease, endocrine combination therapy, dose reduction, and temporary treatment interruption
- Effectiveness variables: progression-free survival as the primary end point, calculated as the time (months) from the start of treatment to the date of progression (assessed by imaging tests) or death
- Toxicity variables: adverse events related to treatment, classified by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[10]

Information was collected from electronic oncology medical records and from the Pharmacy Service's outpatient dispensing registration. The study was approved by each hospital's clinical research ethics committee.

Statistical Analysis

A descriptive analysis was performed, using frequency tables to evaluate the qualitative variables. Quantitative variables were summarized using standard measures of central tendency and dispersion. The Kaplan–Meier method was used to calculate progression-free survival. SPSS software, version 17 (IBM Corporation), was used to perform statistical calculations.

RESULTS

During the study period (April 2017 to September 2019), 53 patients with HR-positive, HER2-negative metastatic breast cancer, all of them women, were treated at the 3 study hospitals. Mean age was 57 years (range 31–87 years). Clinical and demographic characteristics are presented in Table 1.

All of the patients received palbociclib for treatment of metastatic breast cancer. The drug was prescribed as first-line therapy for 23 patients (43%), as second-line therapy for 23 patients (43%), and as third-line or later treatment for 7 patients (13%).

Follow-up data were collected to April 2020. The median duration of palbociclib treatment was 9.1 months (range 1.4–28.0 months), corresponding to a median of 9 cycles (range 2–29), and the median duration of follow-up was 17.5 months (range 7.5–37.1 months). At the end of the follow-up period, 23 (43%) of the women were still receiving palbociclib, whereas 30 had stopped the treatment: 2 because of death, 2 because of toxic effects (one with grade 3 neutropenia and the other with decreased renal function), and 26 because of progression of metastatic disease. The median duration of treatment was 6.0 months (range 1.4–21.7 months) for patients who discontinued palbociclib and 17.0 months (range 7.8–28.0 months) for those who were continuing treatment.

By the end of the follow-up period, overall median progression-free survival with palbociclib therapy was 14.4 months (95% confidence interval [CI] 6.2–22.2 months) (Figure 1).

The 23 women who received palbociclib as first-line treatment did not experience any progression-free survival, and 7 (30%) of these patients stopped treatment: 1 because of death, 2 because of toxic effects, and 4 because of disease progression. Among these patients, median treatment duration was 12.1 months (95% CI 1.4–28.0 months).

Among the 23 patients who received palbociclib as second-line treatment, median progression-free survival was 13.3 months (95% CI 4.1–22.4 months). Sixteen (70%) of these patients stopped treatment: 1 because of death and 15 because of disease progression. In this group of patients, median treatment duration was 8.3 months (range 1.6–28.0 months) (Figure 2).

Among the 7 women who were treated with palbociclib as third-line therapy, median progression-free survival was 6.0 months (95% CI 0.9–11.1 months) (Figure 3), and all of

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients

Characteristic	Type of Therapy; No. (%) of Patients[a]			
	Total (*n* = 53)	First-Line (*n* = 23)	Second-Line (*n* = 23)	Third-Line and Beyond (*n* = 7)
Age (years) (median and range)	57 (31–87)	58 (32–87)	63 (31–80)	54 (42–79)
Stage of menopause				
Before	10 (19)	5 (22)	4 (17)	1 (14)
After	43 (81)	18 (78)	19 (83)	6 (86)
Medication				
Fulvestrant	33 (62)	7 (30)	21 (91)	5 (71)
Letrozole	18 (34)	15 (65)	1 (4)	2 (29)
Exemestane	1 (2)	0	1 (4)	0
Tamoxifen	1 (2)	1 (4)	0	0
Metastatic disease status				
Diagnosed	14 (26)	6 (26)	5 (22)	3 (43)
Recurrent	30 (57)	12 (52)	14 (61)	4 (57)
Unknown	9 (17)	5 (22)	4 (17)	0
Visceral metastasis				
Yes	21 (40)	10 (43)	9 (39)	2 (29)
No	28 (53)	12 (52)	13 (57)	3 (43)
Unknown	4 (8)	1 (4)	1 (4)	2 (29)
ECOG score				
0	19 (36)	5 (22)	11 (48)	3 (43)
1	18 (34)	6 (26)	8 (35)	4 (57)
2	2 (4)	2 (9)	0	0
Unknown	14 (26)	10 (43)	4 (17)	0

ECOG = Eastern Cooperative Oncology Group.
[a]Except where indicated otherwise.

these patients stopped treatment because of disease progression. Table 2 summarizes progression-free survival for all subgroups.

Palbociclib therapy was temporarily interrupted in 22 patients: one because of surgery, another because of dysphagia, and the remaining 20 because of grade 3 or 4 toxic effects. Seven (32%) of these patients required 1 week of discontinuation before receiving cycle 2 of palbociclib therapy. More information about discontinuation can be found in Table 3.

Dose reductions were required in 19 (36%) of the 53 patients. Two patients who received palbociclib as first-line treatment for metastatic disease began with smaller doses because of their age and comorbidities; one of these patients received 100 mg starting with the first cycle and the other received 75 mg. The other 17 patients initially received palbociclib at the usual dose of 125 mg, but the dose had to be reduced in later cycles because of toxic effects. A dose reduction to 100 mg occurred in cycle 2 for 6 patients (35%), in cycle 3 for 4 patients (24%), and in other cycles for the remaining 7 patients (41%). The dose was further reduced to 75 mg for 11 patients, 5 of them (45%) in cycle 4. For one of the patients with a dose reduction to 75 mg, the 100-mg dose was reinstated in later cycles without any toxic effects. Table 3 summarizes the dose reductions in this study population.

Adverse events of any grade were described for 39 patients (74%). For 27 patients (51%), the adverse events were grade 1 or 2, most commonly asthenia (in 12 patients, 23%) and neutropenia (in 10 patients, 19%). Grade 3 or 4 adverse events were reported in 20 patients (38%), all of whom experienced neutropenia. Table 4 shows the severity and prevalence of adverse events in our population.

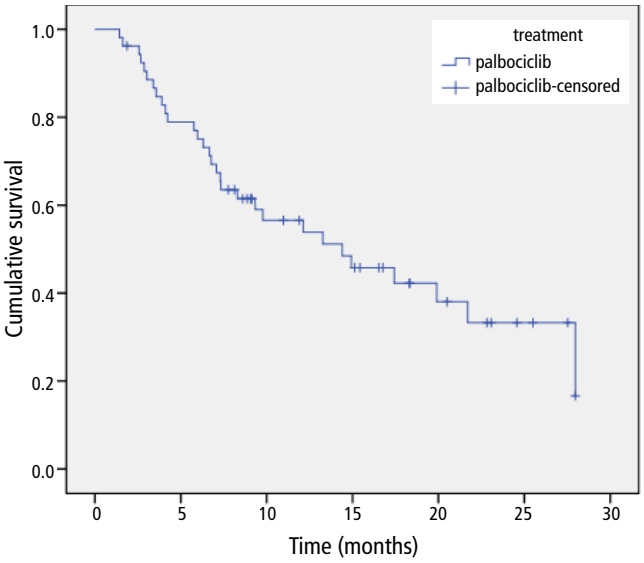

FIGURE 1. Progression-free survival of all patients treated with palbociclib.

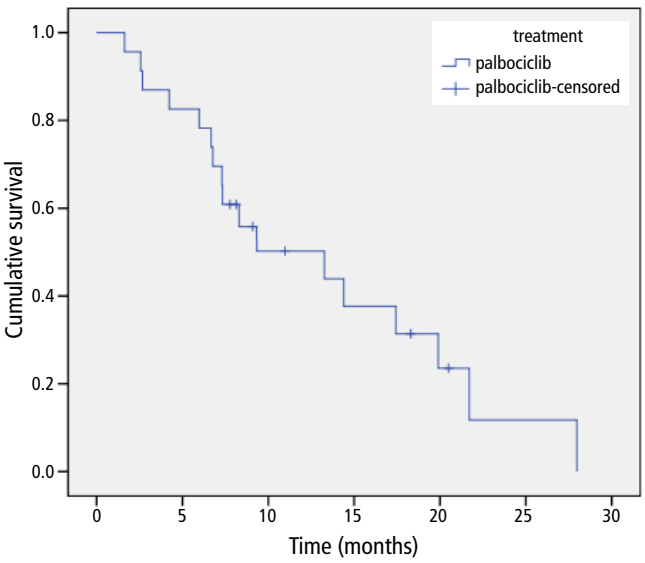

FIGURE 2. Progression-free survival of patients treated with palbociclib as second-line therapy.

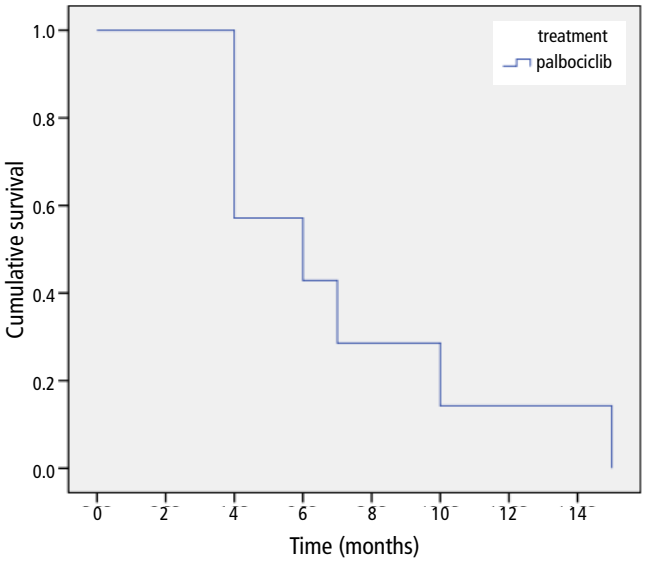

FIGURE 3. Progression-free survival of patients treated with palbociclib as third-line therapy.

TABLE 2. Progression-Free Survival (PFS) by Type of Palbociclib Therapy

Type of Therapy	No. of Patients	No. of Events[a]	Median PFS (months)
All women	53	30	14.4
First-line	23	7	Not reached
Second-line	23	16	13.3
Third-line	7	7	6.0

[a]An "event" was defined as discontinuation of therapy.

TABLE 3. Pharmacotherapeutic Characteristics

Characteristic	Total (*n* = 53)	First-Line (*n* = 23)	Second-Line (*n* = 23)	Third-Line and Beyond (*n* = 7)
	Type of Therapy; No. (%) of Patients			
Temporary treatment suspension				
No	31 (58)	16 (70)	13 (57)	2 (29)
Yes	22 (42)	7 (30)	10 (43)	5 (71)
1 time	11 (21)	2 (9)	7 (30)	2 (29)
2 times	3 (6)	1 (4)	0	2 (29)
≥ 3 times	8 (15)	4 (17)	3 (13)	1 (14)
Dose reduction				
No	34 (64)	14 (61)	16 (70)	4 (57)
Yes	19 (36)	9 (39)	7 (30)	3 (43)
Final dose 100 mg	7 (13)	4 (17)	2 (9)	1 (14)
Final dose 75 mg	12 (23)	5 (22)	5 (22)	2 (29)
Adverse events				
No	14 (26)	9 (39)	5 (22)	0
Yes[a]	39 (74)	14 (61)	18 (78)	7 (100)
Grade 3 or 4	20 (38)	9 (39)	9 (39)	5 (71)
Grade 1 or 2	27 (51)	9 (39)	14 (61)	7 (100)

[a]Some patients experienced multiple adverse events. Therefore, the sums of subgroups are greater than the reported totals.

TABLE 4. Adverse Events Reported (*n* = 53 Patients)

Type of Adverse Event	Grade 3 or 4[a]	Grade 1 or 2[b]
	Grade of Adverse Event; No. (%) of Patients	
Blood and lymphatic system disorders		
Neutropenia	20 (38)	10 (19)
Thrombocytopenia	1 (2)	0
Anemia	1 (2)	7 (13)
Leukopenia	0	1 (2)
Gastrointestinal disorders		
Diarrhea	0	2 (4)
Vomiting/nausea	0	5 (9)
Stomatitis	0	1 (2)
Skin and subcutaneous tissue disorders		
Rash	0	3 (6)
Alopecia	0	1 (2)
General disorders		
Asthenia	0	12 (23)
Muscular pain	0	3 (6)
Investigations		
ALT/AST increased	0	1 (2)
Other		
Onicolysis	0	1 (2)
Subclinical hypothyroidism	0	1 (2)
Mucositis	0	7 (13)
Renal toxicity	1 (2)	0

ALT = alanine aminotransferase, AST = aspartate aminotransferase.
[a]A total of 20 patients experienced grade 3 or 4 adverse events, with some patients experiencing more than one such event.
[b]A total of 27 patients experienced grade 1 or 2 adverse events, with some patients experiencing more than one such event.

DISCUSSION

Prescribing patterns for palbociclib in the 3 study centres were consistent with approved indications. However, the characteristics of women undergoing palbociclib treatment have changed over the years with modification of label indications: initially, palbociclib was used as first-line therapy for metastatic breast cancer in postmenopausal patients, but later it has been used for first- and second-line therapy (or beyond) for pre- and peri-menopausal women.[6,7] Therefore, our population should be assessed according to whether patients received previous treatment for metastatic disease (57%) or not (43%).

Some other studies have included both treatment-naive and previously treated patients. For example, Varella and others[11] studied a cohort of 411 patients, of whom 35.8% received palbociclib as first-line therapy (versus 43% in our study) and 64.3% received the drug as second-line or subsequent therapy (versus 57% in our study). A multicentre Italian study showed a similar distribution: 37.3% of the women received palbociclib as first-line treatment, and 62.7% received the drug as second-line or subsequent therapy.[12] Based on our own review of the literature, we note that receipt of palbociclib as first-line therapy has been less common than its use for subsequent therapy. Kish and others[13] analyzed changes in prescribing patterns for palbociclib in the year after its approval: over that period, the proportion of patients receiving palbociclib as fourth-line or subsequent therapy decreased, and the proportion receiving it as first-line therapy increased. It is probable that in the first few years after their approval, CDK inhibitors were prescribed mainly for women who had received previous lines of treatment, simply because these agents were not available for use during earlier stages of their disease. Thus, with time, we can expect a gradual shift toward first-line use.

The introduction of CDK inhibitors has led to a dramatic change in therapeutic management of patients with metastatic breast cancer, so we expect that more information about patients receiving palbociclib as first-line treatment will become available in the next few years.

The primary objective of our study was to assess progression-free survival. A working group of the Breast Cancer Steering Committee of the National Cancer Institute (US) has recommended progression-free survival as the variable of choice for assessing effectiveness of therapy in metastatic breast cancer when extended post-progression survival is expected.[14] HR-positive, HER2-negative metastatic breast cancer patients receive multiple lines of therapy and are expected to have long post-progression survival, so progression-free survival is considered to be the most robust and appropriate end point in this setting.[14]

Median overall progression-free survival in our study population was 14.4 months. These results were better than those of Pizzuti and others,[12] whose population had median progression-free survival of 12 months. This difference can be explained by a difference between studies in terms of prior treatment: specifically, the proportion of patients who received palbociclib as third-line or subsequent therapy was 22.4% in the Italian study but only 13% in our study.

Women treated with palbociclib as first-line therapy in our study had characteristics similar to those of patients in the PALOMA-2 trial (a phase 3 clinical trial), in which palbociclib and letrozole were administered as first-line therapy.[4] In our study, 65% of the 23 women treated with palbociclib as first-line therapy received letrozole. Progression-free survival was 24.8 months in the PALOMA-2 trial,[4] whereas in our study progression-free survival was not achieved with palbociclib as first-line therapy. However, because we evaluated results from a real-world setting, our population might have included patients not fit enough to participate in clinical trials, leading to these disparate results. Wilkie and others[15] included women treated with aromatase inhibitors as first-line therapy and observed progression-free survival of 26.4 months. The cohort studied by Varella and others[11] included 57 patients treated with palbociclib and letrozole as first-line therapy, who had shorter progression-free survival (15.1 months). In our study, women who received palbociclib as first-line therapy had a median treatment duration of 12.1 months; further study, with longer follow-up, will be required to properly assess progression-free survival in this population.

In an assessment of progression-free survival among previously treated women, updated analyses from the PALOMA-3 study showed progression-free survival of 11.2 months for women who received palbociclib in combination with fulvestrant.[7] In our population, progression-free survival was 13.3 months among women who received palbociclib as second-line therapy, and it decreased further, to 6 months, when palbociclib was administered as third-line treatment. The cohort of Varella and others[11] had a similar decrease in progression-free survival with greater extent of previous treatment: 12.3 months for palbociclib as second-line therapy and 6.4 months for third-line or later therapy. Other real-world studies that included patients with similar characteristics reported shorter progression-free survival: 10 months in the study by Bui and others[16] and 5.8 months in that by du Rusquec and others.[17] This variability may relate to differences in patient characteristics, especially if the analysis focuses on the number of previous treatments for metastatic breast cancer, comorbidities, and performance status. Pizzuti and others[12] concluded that the best outcome was observed when palbociclib was administered early in the course of treatment, and was positively affected by lower ECOG score and absence of visceral metastases, among other factors. In our study, progression-free survival was shorter among patients who received palbociclib with letrozole or fulvestrant as third-line or later treatment than among patients who received palbociclib as first- or second-line therapy.

In scenarios with long post-progression survival, it is important to keep in mind the balance between incremental gain in progression-free survival and the appearance of toxic effects.[14] We measured toxic effects by assessing temporary discontinuations of therapy, dose reductions, and adverse events.

Adverse events of any grade were reported for 74% of our patients. Remarkably, neutropenia was the most common adverse event of any grade. However, the prevalence of any grade of neutropenia was lower than that observed in other cohorts: 57% in our study, 75.9% in the PALOMA-1/TRIO-18 safety analyses,[8] and 95% in the study by Watson and others.[18]

In the expanded analyses of subgroups from the pivotal randomized PALOMA-1/TRIO-18 trial, asthenia, neutropenia, anemia, leukopenia, and alopecia were the most common adverse events (any grade) experienced by patients treated with palbociclib and letrozole, relative to the letrozole arm.[8] All of these adverse events occurred in our study and were mainly reported by our patients as mild or moderate, with asthenia being the most common grade 1 or 2 event. However, adverse events of lesser severity were not well documented in the medical records, as no dose adjustments were required, so they were probably underestimated in our study. Given that most adverse events in our population were grade 1 or 2, we consider palbociclib to have appropriate tolerability and a profile of easily manageable adverse events.

The most frequent (experienced by ≥ 2% of patients) adverse events of grade 3 or above associated with palbociclib and reported in clinical trials (PALOMA-1, PALOMA-2, and PALOMA-3) were neutropenia, infections, leukopenia, fatigue, and anemia. However, in our cohort, only neutropenia exceeded 2% prevalence, with this grade 3 or 4 adverse event being reported for 37% of patients. This prevalence is lower than those observed by Wilkie and others (62%)[15] and by du Rusquec and others (56.7%).[17] A prospective register of adverse events would be useful to obtain accurate information about tolerability in our patient population and to obtain data that would enable us to minimize treatment interruptions and to optimize therapeutic efficacy.

Because of these adverse events, dose delays and reductions were necessary in some cases and were implemented according to the Summary of Product Characteristic.[7] Dose delays were required in 42% of our population, 32% of them before cycle 2 (mainly due to neutropenia). Other studies have reported higher rates of discontinuation: 44% in the cohort of Watson and others[18] and 63% in the cohort of Wilkie and others,[15] the latter having a median time until first delay of 2.3 months.

We found that 36% of patients in our study required dose reductions because of toxic effects. Similarly, the PALOMA trials reported that 34.4% of patients required dose reductions.[7] It is remarkable that in our population, more women required a final dose of 75 mg (23%) than of 100 mg (13%); this trend has not been evident in other studies, where more women required a final dose of 100 mg than 75 mg.[15,18] It should be noted that 23% of patients who received palbociclib as second- or third-line treatment in our study needed a dose reduction to 75 mg, similar to the 22% of those receiving palbociclib as first-line therapy. This might have occurred because previously treated patients were not fit enough to receive the full dose regimen, which could perhaps explain the difference in dose reductions between our study and others. This finding is also curious, given that dose reductions are usually associated with the number of grade 3 or 4 adverse events (those that the Summary of Product Characteristic indicates will lead to temporary interruptions or dose reductions). However, in our cohort, grade 3 or 4 neutropenia was much less frequently reported and the dose reductions were practically the same as those reported in clinical trials; this leads us to think that the trials involved more patients needing dose delays with palbociclib, who recovered quickly, to grade 1 or 2 hematological toxicity, and were therefore able to continue with the next cycle at the same dose. Conversely, in our study, there may have been a greater proportion of patients with grade 4 neutropenia, with an absolute neutrophil count below 0.50×10^9/L, temperature of 38.5°C or above, and/or an infection requiring dose reduction, possibly because when the drug was first introduced in the hospital, patients with more advanced disease were chosen for treatment or because our sample had a higher proportion of previously treated patients.

Some real-world studies have tried to clarify whether there is a difference in progression-free survival with and without dose reductions. Wilkie and others[15] found that dose reductions were required for 56% of the population, a rate higher than what we observed, and concluded that there was no difference in progression-free survival when palbociclib doses were varied. Of the patients in the cohort of Watson and others,[18] 26% required dose adjustments, and no reduction in progression-free survival was associated with lower doses of palbociclib. Thus, monitoring of complete blood count is important to improve tolerance and prolong the duration of the treatment, as reflected in our study.

Our multicentre study provides information about the efficacy and safety of palbociclib in a real-world setting and included patients who would not have been eligible for clinical trials. Our study also assessed 2 different profiles of women: those previously treated for metastatic breast cancer who received palbociclib after failure of other therapeutic approaches and those for whom palbociclib was the first-line treatment. In the coming years, the patient profile will gradually shift to patients without previous treatment, as CDK inhibitors have been shown to be an adequate therapeutic option in this context.

Our study had several limitations. Our primary end point could not be assessed, as progression-free survival was not achieved among patients who received palbociclib as first-line treatment. To improve the robustness of the

results, longer follow-up would be required to obtain results for this subgroup of patients, as well as a longer period of study to increase the size of the cohort. Because the study was retrospective, some information could not be found in the clinical records, which made the safety analysis difficult. Also, we cannot provide data for other CDK inhibitors because palbociclib was the only such medication included in our pharmacotherapeutic guidelines and used in our hospitals, based on efficiency criteria.

CONCLUSION

The development of CDK inhibitors and the introduction into clinical practice of palbociclib, the first agent of this class, represent important additions to the therapeutic armamentarium for HR-positive, HER2-negative metastatic breast cancer. Understanding how this first-in-class CDK inhibitor is used in a real-world patient population, and how drug dosing and monitoring are performed, will aid in the understanding of safe and effective use of the drug. This study provides data from a real-world setting that match previous studies as to effectiveness (measured as progression-free survival) when palbociclib plus endocrine therapy is used as second- or third-line treatment. Longer follow-up is needed to determine its effectiveness as a first-line agent. We consider palbociclib to have appropriate tolerability and a profile of easily manageable adverse events, with none of the patients suspending their treatment because of toxic effects.

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Risk Factors for Preoperative Hyperglycemia in Surgical Patients with Diabetes: A Case–Control Study

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ABSTRACT

Background: Patients with diabetes are more likely to undergo a surgical procedure than the rest of the population, and it is well established that preoperative hyperglycemia is associated with adverse surgical outcomes. However, it is currently unknown what factors increase the odds of preoperative hyperglycemia in people with diabetes.

Objective: To identify patient characteristics that increase the risk of preoperative hyperglycemia.

Methods: This retrospective case–control study compared 100 patients with preoperative hyperglycemia on admission for elective surgery at South Health Campus in Calgary, Alberta (blood glucose > 10.9 mmol/L) with 200 controls who did not have preoperative hyperglycemia on admission for elective surgery (blood glucose ≤ 10.9 mmol/L). Multivariate logistic regression was used to identify risk factors for preoperative hyperglycemia.

Results: In the univariate analysis, age, number of comorbidities, increasing glycated hemoglobin (HbA_{1c}), type of diabetes, type of procedure, and diabetes medications (non-insulin, insulin, both, or none) were associated with increased odds of preoperative hyperglycemia ($p < 0.05$). However, in the adjusted analysis, only increasing HbA_{1c} (odds ratio [OR] 1.69, 95% confidence interval [CI] 1.36–2.12) and type 1 diabetes (OR 4.24, 95% CI 1.11–16.21, relative to type 2 diabetes) were associated with preoperative hyperglycemia.

Conclusions: These results can help clinicians to identify patients who may be at increased risk of hyperglycemia before an elective procedure. They also allow for treatment of those who would benefit most from additional guidance with regard to preoperative glucose management.

Keywords: risk factors, preoperative hyperglycemia, diabetes mellitus, case–control study

RÉSUMÉ

Contexte : Les patients diabétiques sont plus susceptibles que le reste de la population de subir une intervention chirurgicale, et il est bien connu que l'hyperglycémie préopératoire est associée à des résultats chirurgicaux indésirables. Cependant, on ignore actuellement quels facteurs augmentent ce risque chez les personnes atteintes de diabète.

Objectif : Déterminer les caractéristiques des patients qui augmentent le risque d'hyperglycémie préopératoire.

Méthodes : Cette étude cas-témoins rétrospective a comparé 100 patients présentant une hyperglycémie préopératoire à l'admission pour une intervention chirurgicale non urgente au South Health Campus de Calgary, en Alberta (glycémie > 10,9 mmol/L) avec 200 témoins qui n'en présentaient pas (glycémie ≤ 10,9 mmol/L). La détermination des facteurs de risque d'hyperglycémie préopératoire s'est faite par régression logistique multivariée.

Résultats : Dans l'analyse univariée, l'âge, le nombre de comorbidités, l'augmentation du taux d'hémoglobine glyquée (HbA_{1c}), le type de diabète, le type d'intervention et les médicaments contre le diabète (non-insuline, insuline, les deux ou aucun) étaient associés à un risque accru d'hyperglycémie préopératoire ($p < 0,05$). Cependant, dans l'analyse ajustée, seuls l'augmentation de l'HbA_{1c} (rapport de cotes [RC] 1,69; intervalle de confiance [IC] à 95 % 1,36-2,12) et le diabète de type 1 (RC 4,24; IC à 95 % 1,11-16,21, par rapport au diabète de type 2) étaient associés à une hyperglycémie préopératoire.

Conclusions : Ces résultats peuvent aider les cliniciens à repérer les patients qui pourraient présenter un plus grand risque d'hyperglycémie avant une intervention non urgente. Ils permettent également de traiter ceux qui bénéficieraient le plus de conseils supplémentaires en matière de gestion préopératoire de la glycémie.

Mots-clés : facteurs de risque, hyperglycémie préopératoire, diabète sucré, étude cas-témoins

INTRODUCTION

Approximately 10% of Canadians have diabetes, and the incidence of diabetes is expected to grow exponentially, surpassing 12% by 2025.[1] Furthermore, about 20% of Canadians had prediabetes in 2015, meaning that almost one-third of Canada's population is at risk for development of diabetes or already has the disorder.[1] Because people who have diabetes are more likely to undergo surgery than those who do not, a large proportion of surgical patients have diabetes or prediabetes.[2] The World Health Organization has identified 4 key components for reliable perioperative care: antimicrobial

coverage, appropriate removal of hair, perioperative normothermia, and perioperative glucose control.[3] With the growing population of people who have diabetes and prediabetes, perioperative glucose control and the adverse effects of perioperative hyperglycemia are gaining attention.

It is well established that diabetes and elevated preoperative blood glucose levels are associated with adverse outcomes in noncardiac surgery.[4-7] Surgical patients often have their antihyperglycemic medications held or reduced on the day of surgery to avoid hypoglycemia while fasting, which further increases their risk of preoperative hyperglycemia, especially if their surgery is scheduled for later in the day. Noordzij and others[4] demonstrated that preoperative blood glucose levels greater than 11.1 mmol/L and those between 5.6 and 11.1 mmol/L were associated with 2.1-fold and 1.7-fold increased mortality risks, respectively, when compared with normoglycemia. In terms of cardiovascular mortality specifically, these risks increased to 4-fold and 3-fold, respectively.[4] Furthermore, Frisch and others[5] found that patients who died within 30 days after their surgery had significantly higher blood glucose levels before and after the procedure.[5] Perioperative hyperglycemia is also associated with a higher risk for acute myocardial infarction, acute renal failure, urinary tract infection, systemic infection, and postoperative pneumonia, as well as increased lengths of stay both within the hospital and in the intensive care unit (ICU). Finally, for every 1 mmol/L increase in blood glucose before surgery, the risk of death increases by 19%.[4,8]

These findings reinforce the advantage of proactively identifying and planning for possible hyperglycemia in those people at risk, rather than relying upon surgical staff to take an appropriate reactive approach should hyperglycemia occur. Currently, pharmacists providing services in the Pre-Admission Clinic (PAC) of the South Health Campus, Calgary, Alberta, see patients scheduled for elective surgery a few weeks before their procedure and attempt to identify patients with diabetes who may be at increased risk of preoperative hyperglycemia. The PAC pharmacists assess the risk of hyperglycemia using patient history, background knowledge of diabetes, and standard practices regarding management of hypoglycemic medication in preparation for surgery. In turn, the pharmacists prescribe insulin correction scales to be applied for patients whose blood glucose exceeds 10.9 mmol/L when they are admitted before surgery, using calculated insulin sensitivity that targets blood glucose of 9 mmol/L.

To date, very little research has been done to identify risk factors for preoperative hyperglycemia. It has previously been shown that diabetes and duration of surgery are risk factors for intraoperative dysglycemia in elderly patients undergoing elective surgery.[9] Furthermore, in a prospective observational study that included patients with and without diabetes undergoing primary hip or knee replacement, Jämsen and others[10] found that a prior diagnosis of diabetes, higher glycated hemoglobin (HbA_{1c}) and higher fasting glucose on the operative day were associated with postoperative hyperglycemia. Finally, in a retrospective cohort study of children with traumatic brain injuries who underwent craniotomy, age less than 4 years, severe brain injury, and the presence of multiple lesions were risk factors for preoperative, intraoperative, or postoperative hyperglycemia.[11] However, to our knowledge, no study to date has investigated the risk factors for preoperative hyperglycemia in patients with diabetes who are undergoing elective noncardiac surgery. This study therefore fills an important knowledge gap that will ultimately empower clinicians to provide better surgical care, as they will be better able to plan for their diabetic patients' perioperative glycemic control when seeing them in a PAC or similar setting.

METHODS

This case–control study included patients with type 1 or type 2 diabetes who underwent elective surgery at South Health Campus between 2014 and 2019. The cases were defined as patients with preoperative blood glucose above 10.9 mmol/L, and the controls were those with preoperative blood glucose of 10.9 mmol/L or below. Patients were matched, in a 2 to 1 ratio of controls to cases, based on the year of the procedure, to reduce the risk that practice changes related to treatment of hyperglycemia and treatment of diabetes in general would influence any of the findings. Patient identification started with surgical admissions on January 1, 2014, and continued chronologically until each group was populated. The data collectors were not blinded; however, a standardized data collection approach was used, and all data collected were objective, which limited the amount of bias that could be introduced.

Alberta Health Services Analytics (Data Integration, Measurement and Reporting) provided a list of all patients with preoperative blood glucose levels recorded on their surgical chart before surgery at South Health Campus. At this location, only people with a known diagnosis of diabetes undergo preoperative blood glucose testing, which is performed by nursing staff certified to use a point-of-care Accuchek Inform II blood glucose machine (Roche), calibrated once each day. From this list, 100 patients with preoperative blood glucose above 10.9 mmol/L (hyperglycemia) and 200 patients with preoperative blood glucose less than or equal to 10.9 mmol/L (euglycemia) were selected for comparison. Patients' baseline demographic data and characteristics were gathered from electronic charts (Sunrise Clinical Manager).

To be included in the study, patients had to have undergone elective noncardiac surgery between January 1, 2014, and December 31, 2019; had to have a preoperative blood glucose value entered in the surgical chart; and had to have

a documented diagnosis of diabetes, with a record of antihyperglycemic medications, insulin, or the indication of diabetes during their PAC consult. Patients were excluded from the study if they were not seen in the PAC by either an internal medicine or anesthesia provider before the surgery, did not have surgery after their PAC appointment, were missing data for the predetermined characteristics to be compared between the groups, or underwent bariatric surgery (because the current standard for this type of surgery is an all-liquid diet, which drastically changes insulin sensitivity).

Several patient characteristics were compared between the cases and controls in a univariate analysis, specifically sex, age, body mass index, number of comorbidities (as recorded in the PAC consult note), most recent HbA_{1c} (i.e., at the time of the PAC visit), current diabetes medications, use of medications known to cause hyperglycemia, type of procedure, type of diabetes, and preoperative reduction of insulin dose. Categorical variables (sex, medications, type of procedure, type of diabetes, and insulin dose reduction) were analyzed using χ^2 tests, and continuous variables (age, body mass index, number of comorbidities, HbA_{1c}) were analyzed using the *t* test. As a secondary analysis, a multivariate logistic regression analysis that included all variables with statistical significance ($p < 0.05$) in the univariate analysis was performed to determine which patient characteristics remained associated with preoperative hyperglycemia after adjustment. Multicollinearity between variables was assessed, and variables with a variance inflation factor greater than 3 were excluded from the multivariate analysis. The model's goodness of fit was determined by calculating the Nagelkerke R^2 value.[12] The C-statistic was calculated to determine the model's predictive accuracy.[13] SPSS Statistics software (version 25, IBM Corporation) was used to analyze the data.

Ethics approval was granted by the University of Calgary Conjoint Health Research Ethics Board. Given the retrospective nature of the study, it was not feasible to obtain patient consent; therefore, the ethics board also granted a waiver of consent. Appropriate safeguards were put in place to protect the privacy of the patients included in the study.

RESULTS

Altogether, this study included 100 patients with preoperative hyperglycemia and 200 matched controls who did not have preoperative hyperglycemia. To populate these 100 cases and 200 controls, 210 hyperglycemic patients and 418 euglycemic patients were screened, respectively. A baseline description of the cohorts is shown in Table 1. The average preoperative blood glucose level was 13.1 (standard deviation [SD] 1.92) mmol/L among cases and 7.5 (SD 1.50) mmol/L among controls. The case group was younger, had fewer comorbidities, had higher average HbA_{1c} (8.55% [SD 1.25%] versus 7.33% [SD 1.36%]), had a higher proportion of patients with type 1 diabetes (29% versus 3.5%), had higher proportions of patients taking insulin alone or in combination with non-insulin medications, and had lower proportions of patients taking only non-insulin or no hypoglycemic medications. Differences in the types of surgical procedures were also observed, with a lower proportion of cases undergoing elective orthopedic surgery, whereas a lower proportion of controls underwent plastic surgery procedures.

A more detailed breakdown of the proportions of cases and controls who were taking specific classes of diabetes medications is presented in Table 2. Because of collinearity with other characteristics, diabetes medication class was not included in the multivariate regression; instead, a more general breakdown of the types of medications (insulin only, non-insulin only, insulin and non-insulin [concurrent], neither) was included in the multivariate regression analysis.

The multivariate logistic regression analysis was performed with all characteristics from Table 1 that were significantly different between cases and controls (Table 3). The Nagelkerke R^2 value of 0.368 indicated that 36.8% of the variance in the dependent variable was explained by the model.[12] Furthermore, the model had a C-statistic of 0.757, meaning that it correctly classified 75.7% of cases.[13] Patients with type 1 diabetes had 4.24 higher odds (95% confidence interval [CI] 1.11–16.21) of preoperative hyperglycemia, and for every 1% increase in HbA_{1c}, the odds of hyperglycemia increased by 1.69-fold (95% CI 1.36–2.12).

DISCUSSION

In this study of people with diabetes, comparison of patients with and without preoperative hyperglycemia showed that increasing HbA_{1c} and a diagnosis of type 1 diabetes were significantly predictive of preoperative hyperglycemia. HbA_{1c} provides a "snapshot" of glycemic control over the previous 3 months, so it is not surprising that patients with higher HbA_{1c} were at increased risk of preoperative hyperglycemia, given research showing that elevation of HbA_{1c} is positively correlated with elevation of fasting blood sugars.[12,14] Patients with type 1 diabetes have an insulin production disorder, whereas those with type 2 diabetes have at least some endogenous insulin production. Even though the insulin produced in type 2 diabetes is insufficient to meet all metabolic requirements, it may still be enough to cover basic metabolic processes and keep blood sugars in the recommended range of 5 to 10 mmol/L during the fasting preoperative period. Illustrating this theory is research published by Monnier and others[14] and Riddle and others,[15] who showed that among people with diabetes and relatively lower HbA_{1c} (6% to 8%), the postprandial period

TABLE 1 (Part 1 of 2). Comparison of Variables among Study Groups Using Univariate Analysis

Characteristic	Study Group; No. (%) of Patients[a] Cases (*n* = 100)	Controls (*n* = 200)	*p* Value
Preoperative blood glucose (mmol/L) (mean ± SD)	13.1 ± 1.92	7.5 ± 1.50	< 0.001
Sex, female	54 (54.0)	104 (52.0)	0.74
Age (years) (mean ± SD)	55.1 ± 14.1	64.7 ± 33.86	0.001
Weight (kg) (mean ± SD)	91.6 ± 24.1	91.7 ± 19.6	0.97
BMI (mean ± SD)	31.4 ± 7.23	32.5 ± 6.58	0.20
Most recent HbA_{1c} (%) (mean ± SD)	8.55 ± 1.25	7.33 ± 1.36	< 0.001
No. of comorbidities (mean ± SD)	4.86 ± 2.45	5.63 ± 2.50	0.013
Comorbidities			
Hypertension	53 (53.0)	124 (62.0)	0.14
Dyslipidemia	46 (46.0)	109 (54.5)	0.16
Coronary artery disease	12 (12.0)	35 (17.5)	0.22
Obstructive sleep apnea	22 (22.0)	49 (24.5)	0.63
Asthma or COPD	14 (14.0)	38 (19.0)	0.28
Chronic kidney disease	7 (7.0)	23 (11.5)	0.22
Depression or anxiety	10 (10.0)	32 (16.0)	0.16
GERD	25 (25.0)	61 (30.5)	0.32
Osteoarthritis	24 (24.0)	65 (32.5)	0.13
Hypothyroidism	10 (10.0)	33 (16.5)	0.13
Medications			
Systemic steroids[b]	3 (3.0)	5 (2.5)	0.80
Thiazide diuretics[c]	28 (28.0)	53 (26.5)	0.78
Progesterone or estrogen[d]	4 (4.0)	3 (1.5)	0.18
Second-generation antipsychotics[e]	3 (3.0)	6 (3.0)	> 0.99
Procedure classification			0.016
General surgery	19 (19.0)	47 (23.5)	0.38
Orthopedics	45 (45.0)	117 (58.5)	0.027
Plastic surgery	14 (14.0)	12 (6.0)	0.020
Gynecology	11 (11.0)	11 (5.5)	0.08
Ear, nose, throat, otolaryngology	11 (11.0)	13 (6.5)	0.18
Type of diabetes			< 0.001
Type 1	29 (29.0)	7 (3.5)	
Type 2	71 (71.0)	193 (96.5)	
No. of classes of diabetes medications (mean ± SD)			
All patients	1.65 ± 0.78	1.51 ± 0.88	0.18
Type 2 diabetes only[f]	1.90 ± 0.80	1.53 ± 0.89	0.002
No. of classes of diabetes medications			0.17
0	1 (1.0)	15 (7.5)	0.018
1	49 (49.0)	100 (50.0)	0.87
2	36 (36.0)	58 (29.0)	0.22
3	12 (12.0)	22 (11.0)	0.80
4	2 (2.0)	5 (2.5)	0.79
Diabetes medications			< 0.001
Insulin only	39 (39.0)	18 (9.0)	< 0.001
Insulin + non-insulin	27 (27.0)	33 (16.5)	0.032
Non-insulin only	33 (33.0)	134 (67.0)	< 0.001
No diabetes medications	1 (1.0)	15 (7.5)	0.018

TABLE 1 (Part 2 of 2). Comparison of Variables among Study Groups Using Univariate Analysis

Characteristic	Study Group; No. (%) of Patients[a] Cases (*n* = 100)	Controls (*n* = 200)	*p* Value
Reduction of dose of long-acting or intermediate-acting insulin on day before or morning of surgery[g]			0.57
By > 30%	48 (81.4)	33 (76.7)	
By ≤ 30%	11 (18.6)	10 (23.3)	

BMI = body mass index, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disorder, HbA_{1c} = glycated hemoglobin, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Prednisone, methylprednisolone, dexamethasone, hydrocortisone.
[c]Hydrochlorothiazide, indapamide, chlorthalidone, metolazone.
[d]Systemic and/or topical.
[e]Clozapine, olanzapine, risperidone, quetiapine.
[f]*n* = 71 for cases (with hyperglycemia) and *n* = 193 for controls (without hyperglycemia).
[g]*n* = 59 for cases (with hyperglycemia) and *n* = 43 for controls (without hyperglycemia).

TABLE 2. Specific Classes of Diabetes Medications Used by Patients

Glucose-Lowering Therapy	Study Group; No. (%) of Patients[a] Cases (*n* = 100)	Controls (*n* = 200)	*p* Value
Any insulin			
All patients	66 (66.0)	51 (25.5)	< 0.001
Patients with type 2 diabetes[a]	37 (52.1)	44 (22.8)	< 0.001
Long-acting insulin	53 (53.0)	36 (18.0)	< 0.001
NPH insulin	9 (9.0)	7 (3.5)	0.046
Short- or fast-acting insulin	47 (47.0)	21 (10.5)	< 0.001
Insulin pump	2 (2.0)	2 (1.0)	0.48
Premixed insulin	2 (2.0)	5 (2.5)	0.79
Metformin	55 (55.0)	158 (79.0)	< 0.001
Sulfonylurea	14 (14.0)	35 (17.5)	0.44
Meglitinide	8 (8.0)	13 (6.5)	0.63
SGLT2 inhibitor	7 (7.0)	5 (2.5)	0.06
GLP-1 receptor agonist	4 (4.0)	12 (6.0)	0.47
DPP-4 inhibitor	10 (10.0)	21 (10.5)	0.89
Thiazolidinedione	0 (0.0)	6 (3.0)	0.08

DPP-4 = dipeptidyl peptidase 4, GLP = glucagon-like peptide, NPH = neutral protamine Hagedorn, SGLT2 = sodium-glucose cotransporter 2.
[a]For patients with type 2 diabetes only; *n* = 71 for cases (with hyperglycemia) and *n* = 193 for controls (without hyperglycemia).

is when hyperglycemia occurs, whereas in those with higher HbA_{1c} (above 9%), fasting blood sugars are also above the range accepted as normal. Given that people with type 1 diabetes produce no insulin at all, the common recommendation of reducing basal insulin dosage to prevent hypoglycemia while fasting preoperatively may place these people into an insulin deficit sufficient to raise their fasting blood sugars above the normal threshold, which would account for our findings.

Interestingly, patients in our study who presented with preoperative hyperglycemia had a lower total number of reported comorbidities than controls (4.86 versus 5.63,

TABLE 3. Multivariate Logistic Regression Model for Preoperative Hyperglycemia Risk Factors

Variable	Adjusted Odds Ratio (95% CI)		*p* Value
Age	0.98	(0.96–1.01)	0.22
No. of comorbidities	1.00	(0.88–1.13)	0.97
Most recent HbA_{1c}	1.69	(1.36–2.12)	< 0.001
Type 1 diabetes mellitus	4.24	(1.11–16.21)	0.035
Procedure classification			
General surgery	0.67	(0.21–2.09)	0.49
Orthopedics	1.03	(0.37–2.90)	0.95
Plastic surgery	1.13	(0.30–4.26)	0.86
Gynecology	1.51	(0.37–6.09)	0.57
Ear, nose, throat, otolaryngology[a]	–		–
Diabetes medications			
Insulin only	9.33	(0.87–99.88)	0.06
Insulin + non-insulin	8.33	(0.88–79.02)	0.06
Non-insulin only	0.24	(0.03–2.20)	0.20
No diabetes medications[a]	–		–

CI = confidence interval, HbA_{1c} = glycated hemoglobin.
[a]Excluded from multivariate regression by SPSS software because of small sample size.

$p = 0.013$), in addition to a lower, though nonsignificant, incidence of each of the 10 most prevalent comorbid conditions (see Table 1). We attribute these findings to multiple possibilities. One potential explanation is that people with more comorbidities may be deemed "higher risk" for surgery and thus may not be cleared for an elective procedure until better glycemic control has been achieved. For example, someone with previous myocardial infarction or stroke and suboptimal blood sugar control may not be allowed to proceed until their blood sugars are better controlled, whereas poorer glycemic control may be tolerated among those deemed to be "lower risk" with only a few comorbidities. Another possible explanation is that people in the hyperglycemic (case) group were more likely than those in the control group to have type 1 diabetes (29% versus 3.5% prevalence, respectively), a condition that is more prevalent in the younger population who have not lived long enough for other comorbidities to develop. This possible explanation is affirmed by the finding that average age was significantly lower among cases than among controls (55.1 versus 64.7 years).

Patients undergoing a plastic surgery procedure were more likely to have preoperative hyperglycemia, whereas patients undergoing an orthopedic procedure were more likely to have preoperative euglycemia. A possible explanation for the observation relating to plastic surgery procedures is that the risk associated with hyperglycemia might have been accepted by the patient and surgeon because of the perceived urgency of surgery, as these procedures included skin grafts, debridements, and nerve decompressions. The orthopedic procedures (knee, hip, and shoulder arthroscopy) were likely deemed less urgent, making the risk of hyperglycemia less acceptable. People having less urgent elective surgery were likely required to achieve better glycemic control before their procedure was scheduled.

This study had several limitations. Socioeconomic status is an important determinant of health and could not be assessed from the data available. We were unable to assess adherence to prescribed medications and/or preoperative instructions, such as holding of medications before the procedure or adjustment of insulin doses. Data collected were from patients who underwent elective surgical procedures before the widespread use and improved accessibility of the sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) analogues in Alberta, so we were unable to assess the impact of these agents on preoperative hyperglycemia. Because the site only started its surgical program in 2014, we also had a limited number of patients with preoperative hyperglycemia from whom to draw our cases, which limited the statistical power of the study. Finally, some patients may have corrected their hyperglycemia themselves with short-acting insulin before presenting to hospital for their elective procedure. These patients would have presented with euglycemia, whereas they would otherwise have had hyperglycemia.

Our results align with and expand on those of Jämsen and others,[10] who aimed to identify the risk factors for perioperative hyperglycemia following hip and knee replacement. In their prospective observational study of 191 people with osteoarthritis, diabetes was shown to be a significant risk factor for hyperglycemia. Even though the study included

only 36 people with diabetes, there was a trend toward insulin therapy being an independent risk factor for hyperglycemia. All 9 of those who were taking insulin preoperatively presented with hyperglycemia, compared with only 19 of the 27 people treated with oral diabetes medications ($p = 0.06$), similar to the result in our study. Furthermore, a strong association between HbA_{1c} and hyperglycemia was demonstrated, as the risk of hyperglycemia was approximately 4-fold higher among people with HbA_{1c} greater than or equal to 6.5%. Similar to our findings, Jämsen and others[10] showed that none of the self-reported comorbidities were associated with an increased risk of hyperglycemia.

CONCLUSION

Increasing HbA_{1c} and type 1 diabetes were associated with increased odds of preoperative hyperglycemia among people with diabetes undergoing elective surgery after assessment in a preoperative assessment clinic. Further studies with larger groups of patients should be done to identify additional risk factors for preoperative hyperglycemia, especially with the increased use of SGLT2 inhibitors and GLP-1 agonists. It has previously been well established that preoperative hyperglycemia increases the risk of poor postsurgical outcomes, including infection, cardiac complications, renal failure, pneumonia, systemic infections, longer stays in the ICU or the hospital, and death.[4-7] People with preoperative hyperglycemia can logically be assumed to have the highest risk for intraoperative and postoperative hyperglycemia, which are known risk factors for postoperative morbidity and mortality. The information we have presented has real-world applicability and can be used by clinicians in identifying people at increased risk of preoperative hyperglycemia; it also allows for a proactive and informed approach that involves planning for improved surgical glycemic control.

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Health Care Professionals' Perceptions of the Role of the Clinical Pharmacist and Expanded Pharmacist Coverage in Critical Care

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ABSTRACT

Background: During the first wave of the COVID-19 pandemic, coverage by critical care pharmacists (CCPs) was expanded in 2 medical–surgical intensive care units at the Queen Elizabeth II Health Sciences Centre, in Halifax, Nova Scotia, from 8 hours per day, 5 days per week, excluding holidays, to 8 hours per day, 7 days per week, including holidays.

Objectives: To describe health care professionals' opinions about and perceived impacts of the expanded CCP coverage on patient care, as well as their opinions about the role of the CCP as a member of the critical care team.

Methods: An electronic 22-item survey was distributed to critical care health care professionals to capture opinions and perceived impacts of expanded CCP coverage. The perceived importance of 25 evidence-informed CCP activities was assessed using a 5-point Likert scale.

Results: Thirty-eight complete responses were included (15% response rate, based on distribution of the survey to 249 health care professionals). Most respondents agreed or strongly agreed with the following statements: CCPs are integral members of the critical care team (34/38 [89%]), CCPs play an important role in improving patient outcomes (34/38 [89%]), the presence of CCPs on the unit and on patient care rounds allows other health care professionals to concentrate on their own professional responsibilities (33/38 [87%]), and the expanded CCP coverage improved patient care (29/35 [83%]). Respondents most frequently categorized 23 of the 25 CCP activities as very important.

Conclusions: Expanded CCP coverage was perceived to have a positive effect on both patient care and members of the critical care team. Most CCP activities were perceived as very important. Given the findings of this quality project, novel staffing models are being explored to optimize CCP coverage.

Keywords: critical care, expanded pharmacist coverage, pharmacy practice

RÉSUMÉ

Contexte : Au cours de la première vague de la pandémie de COVID-19, la couverture par les pharmaciens de soins intensifs (PSI) a été étendue dans 2 unités de soins intensifs médico-chirurgicaux du Queen Elizabeth II Health Sciences Centre, à Halifax (Nouvelle-Écosse) : de 8 heures par jour, 5 jours par semaine, hors jours fériés, la couverture est passée à 8 heures par jour, 7 jours par semaine, y compris les jours fériés.

Objectifs : Décrire les opinions des professionnels de la santé sur la couverture élargie des PSI et leurs perceptions des incidences de celle-ci sur les soins aux patients, ainsi que le rôle des PSI en tant que membres de l'équipe de soins intensifs.

Méthodes : Un sondage électronique comportant 22 questions a été distribué aux professionnels de la santé en soins intensifs pour recueillir les opinions et les impacts perçus de l›élargissement de la couverture des PSI. L'importance perçue des 25 activités des PSI fondées sur des données probantes a été évaluée à l'aide d'une échelle de Likert à 5 points.

Résultats : Trente-huit réponses complètes ont été incluses (taux de réponse de 15 %, basé sur une distribution de l'enquête à 249 professionnels de la santé). La plupart des répondants étaient d'accord ou fortement d'accord avec les affirmations suivantes : « les PSI font partie intégrante de l'équipe de soins intensifs » (34/38, 89 %); « les PSI jouent un rôle important dans l'amélioration des résultats pour les patients » (34/38, 89 %); « la présence des PSI dans l'unité et lors des tournées de soins aux patients permet à d'autres professionnels de la santé de se concentrer sur leurs propres responsabilités professionnelles » (33/38, 87 %); et « la couverture élargie des PSI a amélioré les soins aux patients » (29/35, 83 %). Les répondants ont le plus souvent classé 23 des 25 activités du PSI comme « très importantes ».

Conclusions : L'élargissement de la couverture des PSI était perçu comme ayant un effet positif à la fois sur les soins aux patients et sur les membres de l'équipe de soins intensifs. La plupart des activités des PSI étaient perçues comme très importantes. Compte tenu des résultats de ce projet de qualité, de nouveaux modèles de dotation en personnel sont à l'étude pour optimiser la couverture des PSI.

Mots-clés : soins intensifs, couverture élargie des pharmaciens, pratique pharmaceutique

INTRODUCTION

At the Queen Elizabeth II Health Sciences Centre (QEII HSC) in Halifax, Nova Scotia, critical care pharmacists (CCPs) provide clinical services to 2 medical–surgical intensive care units (ICUs) 8 hours per day, 5 days per week. The CCPs are integrated members of the critical care team who have specialized training and experience in critical care. They provide pharmaceutical patient care, attend patient care rounds, and provide drug information, education, and support to patients, families, and other health care professionals. On weekends there is no dedicated CCP coverage; instead, pharmacists in the hospital dispensary, who may or may not have critical care training or experience, provide medication distribution services and are available for consultation.

In preparation for a potential increase in the number of patients admitted to the ICUs during the first wave of the COVID-19 pandemic, CCP coverage was expanded to 8 hours per day, 7 days per week, for the period from April 16 to May 31, 2020. This expansion was achieved by having 2 CCPs dedicated to providing clinical coverage to each ICU. The CCPs were not responsible for distribution services during this period.

This project aimed to describe health care professionals' opinions about and the perceived impacts of the expanded CCP coverage on patient care, as well as their opinions about the role of the CCP in critical care.

METHODS

Development of Survey Questionnaire

A 22-question electronic survey, based on previous research[1] and the expertise of team members, was created and built using SelectSurvey (Alberta Health Services). Questions were designed to capture opinions about and the perceived impact of expanded CCP coverage, as well as the perceived importance of various activities within the CCP role. Questions pertaining to the role of the CCP were based on the Society of Critical Care Medicine (SCCM) joint task force position paper on critical care pharmacy services,[2] which delineates the activities of a CCP and the scope of pharmacy services within the critical care unit. The project team created 25 statements based on activities outlined in the position paper to include in the survey. Priority was given to activities relating to the individual role of the CCP (i.e., not system-based) and patient care. Activities were excluded if they were not feasible to offer because of limits on resources available at the time (e.g., bar coding) or would not be changed by the results of the survey (e.g., CCP would continue to use the medical record to communicate with other health care professionals, regardless of the perceived importance of this activity). In addition, several related activities were combined into single statements to minimize the length of the survey. The survey was assessed for face validity and readability by 5 non–critical care health care professionals. The complete survey is available upon request to the corresponding author.

Distribution of Survey Questionnaire

A link to the survey was distributed by email to all health care professionals working in the study ICUs; the distribution included medical residents who completed rotations during the study period. The online survey was open from August 28 to September 25, 2020. Completion of the survey was considered to represent implied consent.

RESULTS

The survey was distributed to 249 health care professionals. Thirty-eight complete responses were received, for an overall response rate of 15%. Incomplete responses were not included in the analysis. Respondents' characteristics are shown in Table 1.

Perceived Impact of Expanded Clinical Pharmacist Coverage

Thirty-five (92%) of the 38 respondents reported working with a CCP during the study period. These respondents

TABLE 1. Characteristics of Respondents

Characteristic	No. (%) of Respondents (*n* = 38)
Health care professional	
Physician	9 (24)
Medical fellow	2 (5)
Medical resident	5 (13)
Nurse	20 (53)
Other[a]	2 (5)
Primary ICU site	
MSNICU	14 (37)
MSICU	7 (18)
Both MSNICU and MSICU	17 (45)
Length of time working in critical care at the QEII HSC (years)	
0–2	10 (26)
3–5	10 (26)
6–10	5 (13)
> 10	13 (34)
Proportion of time spent working clinically in critical care	
≤ 25%	8 (21)
26% to 50%	1 (3)
51% to 75%	2 (5)
> 75%	27 (71)

ICU = intensive care unit, MSICU = medical–surgical intensive care unit, MSNICU = medical–surgical neuroscience intensive care unit, QEII HSC = Queen Elizabeth II Health Sciences Centre (Halifax).
[a]"Other" consisted of 1 pharmacist and 1 respiratory therapist.

most frequently reported consulting a CCP multiple times per day (15 [43%]). Most respondents reported that expanded CCP coverage was helpful to their practice (20 [57%] strongly agreed and 9 [26%] agreed) and improved patient care (18 [51%] strongly agreed and 11 [31%] agreed). Of the 3 respondents who had not worked with a CCP during the study period, 1 felt that expanded CCP coverage would be helpful to their practice, and 2 were neutral. When these respondents were asked whether expanded CCP coverage would improve patient care, 1 respondent strongly agreed and 2 respondents were neutral.

Most respondents agreed or strongly agreed with the following statements: CCPs are integral members of the critical care team (34 [89%]), CCPs play an important role in improving patient outcomes (34 [89%]), and the presence of CCPs on the unit and on patient care rounds allows other health care professionals to concentrate on their own responsibilities (33 [87%]).

In free-text responses, respondents commented that CCP coverage 7 days per week facilitated timely dose adjustments for renal function, identification and resolution of drug interactions, re-initiation of home medications, optimization of opioid and sedative regimens, the establishment of appropriate stop dates for antimicrobials, and transition to enteral medications when appropriate. The expanded coverage was also noted to ensure continuity of care, given frequent transitions of physician teams.

Availability of CCPs

When respondents were asked how many days per week CCPs should be present in the ICU, 30 (79%) indicated 7 days per week. When asked how many hours per day CCPs should be present in the ICU, the most frequent response was 8 hours (15 [39%]).

Role of CCPs

Respondents were asked to rank the importance of CCPs performing 25 patient care, interprofessional, administrative, and research activities, using a 5-point Likert scale from 1 (not important) to 5 (very important). Respondents most frequently categorized 23 of the 25 CCP activities as very important (Figure 1).

DISCUSSION

Expanded Coverage by CCPs

Overall, the results demonstrated that members of the critical care team see the value of CCPs and perceived that their presence in the ICU 7 days per week provided additional value.

The benefits of including CCPs in critical care teams are supported by the literature. A systematic review and meta-analysis[3] showed that having a CCP as part of the critical care team was associated with a significant reduction in mortality (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.73 to 0.83) and length of stay in the ICU (mean difference –1.33 days, 95% CI –1.75 to –0.90 days) for mixed medical–surgical ICUs. In addition, there were significant reductions in the prevalence of preventable and nonpreventable adverse drug events (OR 0.26, 95% CI 0.15 to 0.44, and OR 0.47, 95% CI 0.28 to 0.77, respectively).

Research has also shown that CCPs can reduce health care expenditures through cost avoidance, mostly through the prevention of adverse drug events.[4-6] Additionally, CCPs have been found to have a return-on-investment ratio of approximately 25:1, and it has been suggested that this is likely an underestimate because the cost savings associated with reductions in mortality and ICU length of stay were not included.[4,7]

The American College of Critical Care Medicine recommends that an intensivist-led multidisciplinary team is the ideal model of care in the ICU and states that "critical care pharmacy and pharmacist services are essential".[8] As medication experts, CCPs are the ideal team members to be proactively involved in guiding and monitoring drug therapy.[7,9]

Role of the CCP

The SCCM joint task force has categorized CCP activities by the level of institutional critical care services offered.[2] Foundational activities are deemed essential to critical care practice and are the core of critical care pharmacy services. Desirable activities are those that are thought to be "value added" and that expand pharmacists' scope of practice. The QEII HSC ICUs met the SCCM joint task force definition of level I ICU and therefore had the highest level of expectation for CCP activities.

When asked how important it was for CCPs to participate in the 22 foundational activities included, respondents most frequently indicated that all but 2 were very important. In terms of these exceptions, respondents most frequently responded that CCPs performing independent patient assessments was slightly important and that CCPs attending and participating in resuscitation events was not important or slightly important. Both of these activities are considered to be foundational activities for CCPs practising in a level I ICU.[2] This mismatch between the opinions of local health care professionals and the SCCM joint task force recommendations may be because these are not activities in which the CCPs at the QEII HSC have historically participated.

When asked to rate the importance of CCPs independently prescribing medications within their scope of practice, responses trended toward this activity being important or very important; however, the responses were diverse. New legislation in Nova Scotia has granted pharmacists the authority to independently prescribe for approved minor and common ailments, preventive medicines, a diagnosis

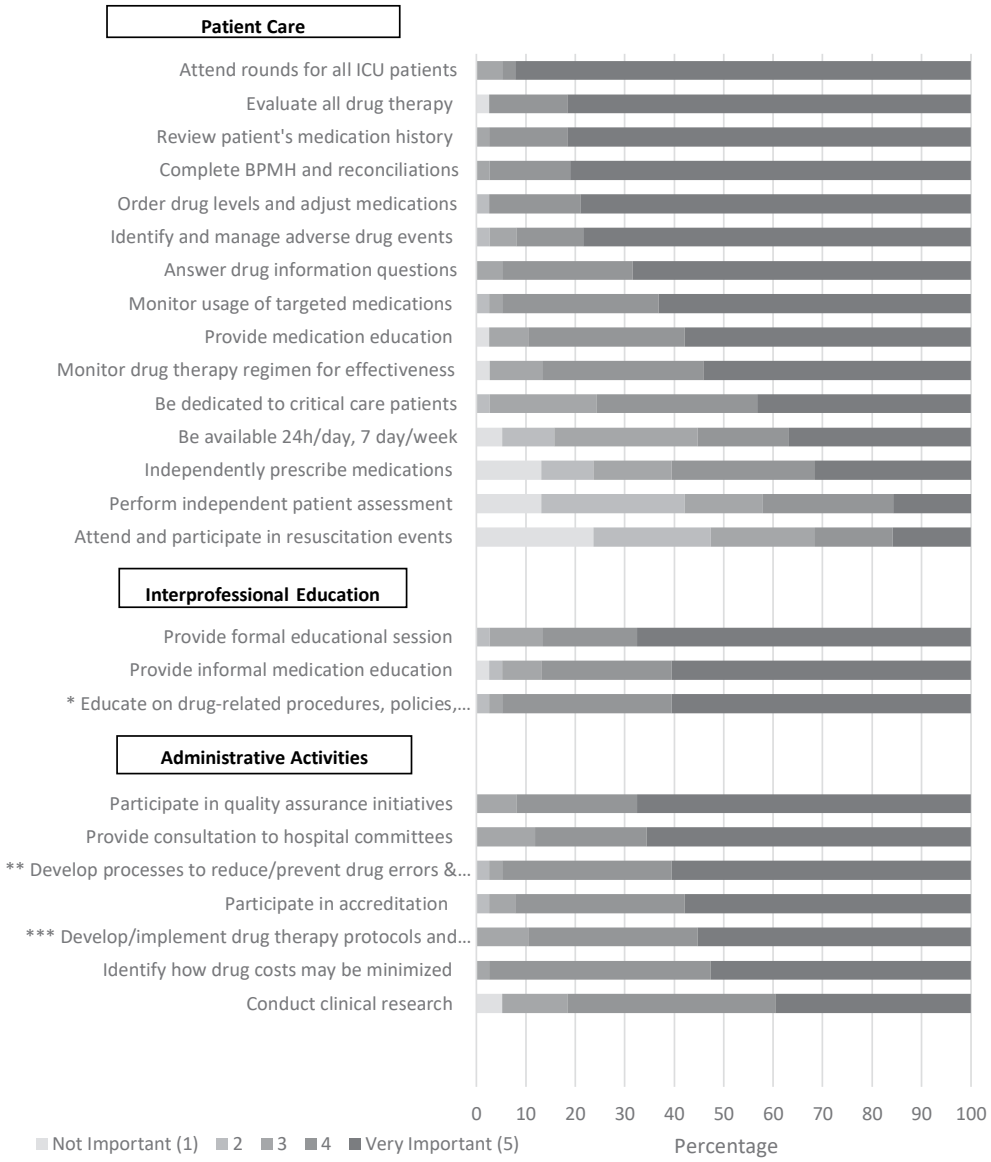

FIGURE 1. Perceived importance of critical care clinical pharmacist activities. *Educate on drug-related procedures, policies, guidelines, and pathways. **Develop processes to reduce/prevent drug errors and adverse drug events. ***Develop or implement drug therapy protocols and pathways. BPMH = best possible medication history, ICU = intensive care unit.

provided by a primary care provider or specialist, and a diagnosis supported by a protocol.[10] Recent policy changes within Nova Scotia Health have expanded hospital pharmacists' prescribing authority to be consistent with the new legislation and standards of practice. This variation in perception of the importance of CCPs participating in independent prescribing may signify that more education is required on the role of pharmacists' prescribing.

Limitations

One limitation of this survey was the overall response rate of 15%. A low response rate may limit the generalizability of the results. However, 9 of 14 critical care staff physicians and 2 of 5 critical care fellows completed the survey, for response rates of 64% and 40%, respectively, for these groups. Therefore, we feel the results are generalizable to the local group of critical care physicians as a whole.

CONCLUSION

Expanded CCP coverage was perceived to have a positive impact on both patient care and members of the critical care team. Overall, respondents most frequently thought that the foundational activities of the CCP were very important. Given the findings of this quality project, novel staffing models are being explored to optimize CCP coverage. Education is needed with regard to CCPs participating in more expanded roles, such as performing independent

patient assessments, attending and participating in resuscitation events, and prescribing.

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Levetiracetam for Status Epilepticus in Adults: A Systematic Review

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ABSTRACT

Background: Status epilepticus (SE) is a neurologic emergency with potential for substantial mortality and morbidity. Parenteral benzodiazepine is the established first-line treatment but fails to control SE in about one-third of patients. Levetiracetam may be used for SE that is refractory to benzodiazepine therapy.

Objective: To examine, by means of a systematic review, the role of IV levetiracetam for the treatment of SE in adults.

Data Sources: MEDLINE, Embase, CENTRAL, and CINAHL databases were searched, from inception to August 18, 2020.

Study Selection and Data Extraction: Included in this review were prospective randomized controlled trials comparing levetiracetam with another antiepileptic drug, given with or after a benzodiazepine, in adult patients with SE. The primary outcome was cessation of SE. Quality of evidence was assessed with the Cochrane risk-of-bias tool. Characteristics of the included studies were reported using descriptive statistics.

Data Synthesis: Five studies compared IV levetiracetam with valproic acid, phenytoin (or its prodrug fosphenytoin), or both. All 5 studies found no statistically significant differences in efficacy or safety end points. There were numerically more cases of hypotension and respiratory failure with phenytoin, and more cases of psychiatric adverse effects (e.g., post-ictal psychosis) with levetiracetam.

Conclusions: Available evidence suggests that levetiracetam is as effective as valproic acid or phenytoin for the cessation of SE in adults. Other factors should therefore dictate the choice of antiepileptic drug for patients with SE, such as adverse effect profile, logistics of administration, drug cost, inclusion on hospital formularies, and drug availability.

Keywords: status epilepticus, seizures, levetiracetam, anticonvulsants, systematic review

RÉSUMÉ

Contexte : L'état de mal épileptique (EME) est une urgence neurologique qui s'accompagne d'un potentiel important de mortalité et de morbidité. La benzodiazépine parentérale est le traitement de première ligne établi, mais ne parvient pas à contrôler l'EME chez environ un tiers des patients. Le lévétiracétam peut s'utiliser pour les EME réfractaires au traitement par les benzodiazépines.

Objectif : Examiner, au moyen d'une revue systématique, le rôle du lévétiracétam IV pour le traitement de l'EME chez l'adulte.

Sources des données : Les bases de données MEDLINE, Embase, CENTRAL et CINAHL ont fait l'objet d'une recherche, depuis leur création jusqu'au 18 août 2020.

Sélection des études et extraction des données : Cette revue comprenait des essais contrôlés randomisés prospectifs comparant le lévétiracétam à un autre médicament antiépileptique, administré avec ou après une benzodiazépine, chez des patients adultes atteints d'EME. Le critère de jugement principal était l'arrêt de l'EME. La qualité des preuves a été évaluée avec l'outil de risque de biais Cochrane. Les caractéristiques des études incluses ont été rapportées à l'aide de statistiques descriptives.

Synthèse des données : Cinq études ont comparé le lévétiracétam IV avec l'acide valproïque, la phénytoïne (ou son promédicament, la fosphénytoïne), ou les deux. Les 5 études n'ont trouvé aucune différence statistiquement significative en termes d'efficacité ou d'innocuité. Numériquement, les cas d'hypotension et d'insuffisance respiratoire avec la phénytoïne étaient plus élevés, et les cas d'effets indésirables psychiatriques (par exemple, psychose post-critique) étaient plus élevés avec le lévétiracétam.

Conclusions : Les preuves disponibles suggèrent que le lévétiracétam est aussi efficace que l'acide valproïque ou la phénytoïne pour l'arrêt de l'EME chez l'adulte. D'autres facteurs devraient donc dicter le choix du médicament antiépileptique pour les patients atteints d'EME, tels que le profil des effets indésirables, la logistique d'administration, le coût du médicament, l'inscription sur les formulaires hospitaliers et la disponibilité des médicaments.

Mots-clés : état de mal épileptique, convulsions, lévétiracétam, anticonvulsivants, revue systématique

INTRODUCTION

Status epilepticus (SE) is a neurologic emergency with substantial mortality and morbidity if not treated promptly.[1] It is also a cost-intensive condition for health care systems, with one study estimating the direct cost in the United States as $4 billion annually.[2] Parenteral administration of a benzodiazepine (usually lorazepam, midazolam, or diazepam) is the established first-line treatment; however, benzodiazepine therapy may fail to control SE in approximately one-third of patients.[3] Reasons for failure of benzodiazepines to control prolonged SE may include an increased rate of internalization of γ-aminobutyric acid (GABA) receptors during seizure activity.[4]

Ongoing seizure activity requires treatment with medications that act on a variety of receptors and ion channels to increase inhibition and decrease excitation of the neurons.[5] In patients whose SE is uncontrolled despite receiving benzodiazepines, guidelines recommend antiepileptic drugs (AEDs), including IV levetiracetam, valproic acid, phenytoin, or fosphenytoin, a prodrug of phenytoin.[6] Guidelines do not indicate an evidence-based preference for any particular AED.[6,7]

Oral levetiracetam is frequently used for the preventive management of epilepsy, and there is evidence to support its use for a variety of seizure types, including monotherapy for partial onset or generalized tonic-clonic seizures.[8] Compared with other AEDs, levetiracetam has several potential benefits: high oral bioavailability, low plasma protein binding, and a lack of cytochrome P450 drug interactions.[8] The parenteral version of levetiracetam was only recently (in October 2019) approved and marketed in Canada, despite having been available in other countries for several years.[9]

Levetiracetam has a novel structure and multiple proposed mechanisms of action that distinguish it from other available AEDs. Although not yet well understood, its proposed main mechanism is binding to synaptic vesical protein 2A, which consequentially reduces the presynaptic release of neurotransmitters and vesicular transport of calcium ions (Ca^{2+}).[5,8] In addition, levetiracetam has indirect effects on levels of intraneuronal Ca^{2+} and GABA modulation.[7,9] It has no direct effects on sodium channels or GABA receptors, the main mechanism of action of many other AEDs.[7,9]

The objective of this review was to determine whether, in adult patients with SE refractory to benzodiazepines, levetiracetam was more effective in the control of seizures than other AEDs.

METHODS

Search Strategy and Study Selection

MEDLINE, Embase, CENTRAL, and CINAHL databases were systematically searched from their inception to August 18, 2020, as outlined in Appendix 1 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/207). The search terms were "levetiracetam", "status epilepticus" or "epileptic state", and "randomized controlled trial". Results were limited to human participants. No language restrictions were applied. Conference proceedings from the databases searched were included in the screening process. The search was supplemented by reviewing the reference lists of relevant articles. A request for unpublished data from the brand name manufacturer was unsuccessful. One author (C.A.W.) screened the title and abstract of each identified article for inclusion or exclusion in the systematic review. Eligible studies were prospective randomized controlled trials (RCTs) that included adult patients with SE. Studies were included if they compared levetiracetam with another AED, given concurrently with or after a benzodiazepine.

Our primary outcome of interest was cessation of SE. The quality of evidence was assessed independently by 2 authors (C.A.W. and E.D.O.) using the Cochrane risk-of-bias tool.[10] Any disagreement was resolved through discussion until a consensus was reached. Characteristics of the included studies were reported using descriptive statistics. No quantitative synthesis of the evidence (i.e., meta-analysis) was performed.

RESULTS

The literature search yielded 92 records, of which 5 met our criteria and were included in this review.[11-15] The study flow diagram is shown in Figure 1. Most exclusions were due to the age of participants (pediatric only) or the study design (not clinical trials). The included studies compared IV levetiracetam with phenytoin, fosphenytoin, or valproic acid. In all included studies, the patients had received a benzodiazepine first, except in the study by Gujjar and others,[13] in which only 77% of patients received benzodiazepines. That study was included in the review anyway, because it was felt to be relevant despite the limitations in its methodology. A summary of the included trials is presented in Table 1.

Each of the 5 studies included in this systematic review found no evidence to show superiority of either levetiracetam, phenytoin/fosphenytoin, or valproic acid for cessation of SE. The studies reported various secondary outcomes, none of which showed any statistically significant differences.

In the unblinded, prospective study by Chakravarthi and others,[11] patients were randomly assigned to receive levetiracetam or phenytoin if seizures were uncontrolled after administration of lorazepam. Patients were excluded if they were already taking the study drug, had a history of allergy to any of the study drugs, or had seizures upon drug withdrawal. No power calculation for study size was reported. Baseline characteristics were statistically similar between the phenytoin and levetiracetam groups, with mean ages of 32 and 39 years and past history of epilepsy

in 67% and 77% of patients, respectively. In numeric terms, the mean duration of SE episodes was longer in the phenytoin group (72.05 minutes versus 55.91 minutes), and the incidence of remote etiology was higher (55% versus 27%). However, as shown in Table 1, there was no difference in the control of SE between these agents. There were also no statistically significant differences in any of the secondary outcomes. Seizures recurred within 24 hours in 41% (n = 9/22) of the levetiracetam group and 27% (n = 6/22) of the phenytoin group (p = 0.34). For purposes of this systematic review, the seizure recurrence result was confirmed with the study's lead author, as there was a discrepancy in their manuscript (specifically, an error in their Table 2). A good final neurologic outcome at discharge, defined as Functional Independence Measure score of 5 to 7, was reported in 86% (n = 19/22) of the patients taking levetiracetam and 82% (n = 18/22) of those taking phenytoin (p = 0.68). The mortality rate was the same in the 2 groups, at 9%. No adverse effects were reported with levetiracetam, whereas 9% (n = 2/22) of patients treated with phenytoin experienced hypotension.

In their unblinded, prospective randomized controlled study, Mundlamuri and others[12] recruited patients who presented to the neurologic emergency service with SE. The patients were randomly assigned to receive phenytoin, valproic acid, or levetiracetam as the first-line AED following lorazepam 0.1 mg/kg administered as an IV bolus dose. Patients were excluded if they had nonconvulsive SE; had a hepatic, renal, or cardiac disorder; were pregnant; had a neurosurgical disorder requiring urgent surgical intervention; had a known allergy to any of the AEDs; or had received parenteral AEDs before study entry. Patients who were taking oral AEDs leading up to the SE event were included. Patients were assessed for seizure cessation 30 minutes after completion of the first infusion. If the first agent failed, patients were given one of the alternative AEDs. In the case of failure of the second-line drug, patients were given whichever agent they had not yet received (as third-line treatment). The sample size was chosen based on site feasibility over 38 months. Baseline characteristics were similar among the groups, with mean age 33 to 35 years, a past history of seizures in 50% to 66% of patients, and mean duration of SE of 6.7, 7.38, and 10.18 hours in the phenytoin, valproic acid, and levetiracetam groups, respectively. There were no statistically significant differences between

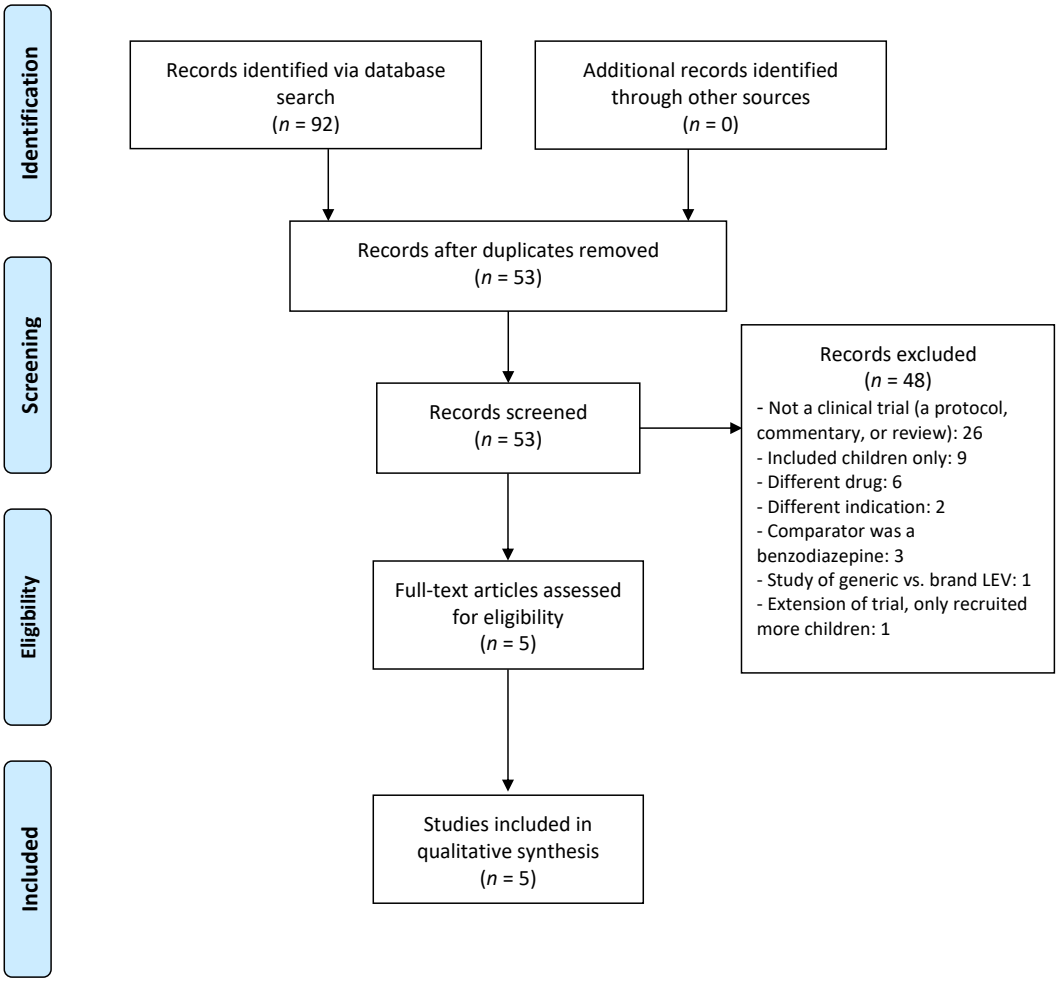

FIGURE 1. Study flow diagram. LEV = levetiracetam.

TABLE 1. Randomized Controlled Trials of Levetiracetam versus Other Antiepileptic Agents for Status Epilepticus

Study	No. of Patients	Study Population	Interventions	Primary Outcome	Results
Chakravarthi et al. (2015)[11]	44	GCSE (defined as lasting > 5 min or as ≥ 2 seizures during which patient does not regain normal sensorium) uncontrolled with lorazepam 0.1 mg/kg IV Age range 14–75 years	PHT 20 mg/kg IV (n = 22) LEV 20 mg/kg IV (n = 22)	Clinical termination of seizure activity within 30 min	PHT: 68.2% (15/22) LEV: 59.1% (13/22) (p = 0.53)
Mundlamuri et al. (2015)[12]	150	GCSE (defined as lasting ≥ 10 min or as ≥ 2 discrete seizures without complete recovery of consciousness in between) Study drug given within 10 min after lorazepam 0.1 mg/kg IV Age range 15–65 years	PHT 20 mg/kg IV (n = 50) VPA 30 mg/kg IV (n = 50) LEV 25 mg/kg IV (n = 50)	No recurrence of seizures after 30 min	PHT: 68.0% (34/50) VPA: 68.0% (34/50) LEV: 78.0% (39/50) (p = 0.44)
Gujjar et al. (2017)[13]	115	GCSE (defined as lasting > 5 min or recurrent with no regaining of consciousness between seizures) or cluster attacks of seizures (defined as ≥ 2 partial or generalized seizures with return of consciousness in between), after IV administration of lorazepam 4 mg or diazepam 5–10 mg in patients with observed ongoing seizures SE group: n = 52 Age > 15 years	*SE group:* PHT 20 mg/kg IV (n = 30) LEV 30 mg/kg IV (n = 22)	Control of SE = cessation of seizure with no recurrence over 24 h and improvement in mental status	*SE group:* PHT: 73.3% (22/30) LEV: 81.8% (18/22) (p = 0.33)
Nene et al. (2019)[14]	118	GCSE (defined as lasting > 5 min or as ≥ 2 seizures without full recovery of consciousness in between) after receiving lorazepam 0.1 mg/kg IV (4–6 mg) Age > 60 years	SVP 20–25 mg/kg IV (n = 60) LEV 20–25 mg/kg IV (n = 58)	No seizure recurrence after 30 min + improvement in level of sensorium in next 24 h, or if sensorium did not improve but EEG showed no NCSE	SVP: 68.3% (41/60) LEV: 74.1% (43/58) (p = 0.49)
Kapur et al. (2019)[15]	384	Convulsive SE unresponsive to benzodiazepines, 5–30 min after dose of benzodiazepine Age > 2 years	LEV 60 mg/kg IV (n = 145) fPHT 20 mg/kg IV (n = 118) VPA 40 mg/kg IV (n = 121)	Absence of clinically evident seizures and improvement in the level of consciousness by 60 min	LEV: 46.9% (68/145) fPHT: 44.9% (53/118) VPA: 46.3% (56/121) No statistically significant differences

EEG = electroencephalography, fPHT = fosphenytoin, GCSE = generalized convulsive status epilepticus, LEV = levetiracetam, NCSE = nonconvulsive status epilepticus, PHT = phenytoin, SE = status epilepticus, SVP = sodium valproate, VPA = valproic acid.

groups in the primary outcome of SE control with the first-line AED. With the sequential approach to treatment, 71.3% (107/150) of the patients experienced seizure control with the first AED, 86.7% (130/150) with the addition of a second agent (if needed), and 92% (138/150) with the third agent, despite the extended duration of SE. Statistical analysis was not done between subgroups of AEDs given as second- or third-line therapy because of small numbers. A good functional outcome at discharge, defined as modified Rankin score of 0 to 3, was reported in 74% (n = 37/50) of patients given phenytoin first, 78% (n = 39/50) of those given valproic acid first, and 86% (n = 43/50) of those given levetiracetam first (p = 0.32). Mortality rates were 12%, 8%, and 10% for the phenytoin, valproic acid, and levetiracetam groups, respectively (p = 0.94). One patient in the phenytoin group suffered cardiac arrest and 2 experienced hypotension; the valproic acid group had no reported adverse events, and the levetiracetam group had 3 patients with post-ictal psychosis (p = 0.25).

The open-label, prospective single-centre study by Gujjar and others[13] examined both patients with generalized convulsive SE (GCSE) and those with cluster seizures. For the purposes of this review, only the results from the GCSE group were included. The exclusion criteria were known allergies, acute cardiac or pulmonary contraindications, imminent neurosurgery, pregnancy, and less obvious

forms of seizures (e.g., pseudoseizures and seizures without overt convulsions). Patients received IV benzodiazepine if ongoing seizures were evident (77%), and were then randomly assigned to receive phenytoin 20 mg/kg or levetiracetam 30 mg/kg in an open-label fashion. No power calculation was performed; rather, a convenience sample size of 100 patients was chosen (52 of whom were included in this analysis of patients with GCSE). Numerically more patients in the phenytoin group required management in the intensive care unit (ICU), had abnormal imaging results, had a Sequential Organ Failure Assessment score of 4 or above, and received IV benzodiazepine. Epilepsy accounted for 56% of the SE cases, of which two-thirds were likely due to non-adherence to medications. However, prior use of AEDs was not described. The primary outcome of SE control, defined as cessation of seizures with improvement in mental status and no recurrence of seizures over 24 hours, occurred with similar frequency in the phenytoin and levetiracetam groups (Table 1). Study protocol violations occurred in 5 patients in each group, whereby patients were given the alternative AED at the discretion of the treating physician. Both intention-to-treat and per protocol analyses were reported, with similar results (per protocol results for SE control: 76% [19/25] with phenytoin, 82% [14/17] with levetiracetam). If patients had a recurrence of seizures within 24 hours, a repeat dose of the initial AED was given, followed by administration of the alternative AED if required for further seizures. In the case of sequential use, all but 4 patients achieved SE control. No significant differences were seen between the groups with respect to poor functional outcome at discharge ($p = 0.29$) or mortality. Two patients in each group reported adverse events: transient hypotension was documented by 2 patients in the phenytoin group, whereas 1 case of transient thrombocytopenia and 1 case of agitation were reported in the levetiracetam group.

In a prospective, single-centre, single-blind trial, Nene and others[14] randomly assigned adults over 60 years of age with GCSE to receive either valproic acid or levetiracetam after an initial dose of lorazepam 0.1 mg/kg IV. The authors specifically wanted to study an elderly population because of the lack of existing evidence in this age group. Patients who had renal, liver, or cardiac disease, those with allergies to either of the study medications, and those who had received any parenteral treatment for the index episode of SE before arrival at the study site were excluded. No power calculation for study size was reported. Given the inclusion criteria, the mean age of participants was 68 years, which represents a much older population than in the other studies. Analysis of the baseline characteristics revealed several differences between the groups, with more patients in the valproic acid group having hypertension, alcohol abuse, and a past history of stroke. Patients presenting to the study site had ongoing seizures for a mean duration of 5.5 hours, and the cause of seizures was unknown in approximately half. The primary outcome of control of SE, defined as no recurrence of seizures after infusion of study drugs and significant improvement in symptoms or electroencephalographic changes within 24 hours, was not significantly different between the groups (86% versus 76% for levetiracetam and valproic acid, respectively; $p = 0.202$). Interestingly, among patients who did not experience cessation of seizures (the primary outcome), 50% (6/12) experienced subsequent control when levetiracetam was added to valproic acid, whereas only 14% (1/7) did so when valproic acid was added to levetiracetam. This difference was not significant, but the comparison may have been underpowered. No significant differences were seen in duration of hospital stay, modified Rankin score at discharge, or death at 30 days. The mortality rates were 22.4% and 18.1% among patients who received valproic acid and levetiracetam, respectively ($p = 0.927$). The only adverse effect noted by the authors was evidence of hepatic dysfunction on day 3 for 1 patient in the valproic acid group.

In the largest prospective, randomized study in our review (and the only multicentre, double-blinded trial), by Kapur and others,[15] patients aged 2 years or older were randomly assigned to 1 of 3 treatment arms: levetiracetam 60 mg/kg, fosphenytoin 20 mg/kg (phenytoin equivalent), or valproic acid 40 mg/kg. Patients were recruited from 57 hospital emergency departments in the United States. The primary exclusion criteria were having a seizure precipitant of major trauma, anoxic brain injury, or hypo- or hyper-glycemia; having already received an AED for the index episode of SE; or being pregnant or incarcerated. A power calculation showed that a maximum of 720 patients would be required; however, the trial was stopped after enrolment of 400 visits (by 384 unique patients) based on a predefined stopping rule for the futility of finding one drug to be superior or inferior. Baseline characteristics were similar among all 3 groups, with mean age of approximately 33 years and a history of epilepsy in 67% to 69% of patients. The median duration of seizure at enrolment was approximately 60 minutes. No treatment was found to be superior to the others for the primary outcome of seizure cessation and improved level of consciousness at 60 minutes without the use of other anticonvulsants. Approximately half of the patients had a response to each of the 3 treatments. Efficacy results were comparable between the intention-to-treat, per-protocol, and adjudicated-outcomes analyses. A post hoc analysis of patients with a response to treatment showed that seizure cessation within 20 minutes was also not significantly different among the groups (77.9% with levetiracetam, 81.1% with fosphenytoin, and 78.2% with valproic acid). The authors reported on the time from the start of the study drug infusion to seizure cessation, although these data were available for only 10% of patients enrolled (those with an audio recording of the clinical event available to corroborate the documented time of seizure cessation). There was no statistically significant difference among

groups, and the median times ranged from 7 minutes in the valproic acid group to 10.5 and 11.7 minutes in the levetiracetam and fosphenytoin groups, respectively. Rates of ICU admission were approximately 60%, regardless of treatment group. The length of ICU stay was also similar, with a median of 1 day for all groups. There was no statistically significant difference in mortality among the groups, with rates of 4.7% for the levetiracetam group, 2.4% for the fosphenytoin group, and 1.6% for the valproic acid group. Similarly, no statistically significant differences in adverse effects were found. The most commonly reported adverse effects were a need for endotracheal intubation (20% for the levetiracetam group, 26.4% for the fosphenytoin group, and 16.8% for the valproic acid group) and acute respiratory depression (8% for the levetiracetam group, 12.8% for the fosphenytoin group, and 8% for the valproic acid group), which may have been secondary to treatment with benzodiazepines or the seizures themselves, rather than the AEDs. No other adverse effects occurred in more than 10% of patients, which supports the safety of the higher doses given. There was numerically, but not statistically, more encephalopathy reported with levetiracetam than with phenytoin or valproic acid (2.7%, 0%, and 0.8%, respectively).

The risk-of-bias assessment is summarized in Table 2, with complete details provided in Appendix 2 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/207). The study by Kapur and others[15] had a low risk of bias, whereas all other studies were ranked as having a high risk of bias because of incomplete blinding. The studies by Chakravarthi and others[11] and Gujjar and others[13] also had poor randomization methodology, the study by Chakravarthi and others[11] had a risk of selection bias due to inadequate allocation concealment, and the study by Mundlamuri and others[12] had missing data that were not clearly addressed.

DISCUSSION

Previous systematic reviews have examined the comparative efficacy of antiepileptic agents in SE. A 2014 meta-analysis[16] of results from 23 articles found that the rates of seizure cessation were as follows: with levetiracetam, 68.5% (95% confidence interval [CI] 56.2%–78.7%); with phenobarbital, 73.6% (95% CI 58.3%–84.8%); with phenytoin, 50.2% (95% CI 34.2%–66.1%); and with valproic acid, 75.7% (95% CI 63.7%–84.8%). Although phenytoin appeared to have lower efficacy, this result was not statistically significant, and all of the CIs were wide. However, the articles included in the meta-analysis were mostly retrospective reports, with only 1 RCT included. A 2016 direct and indirect meta-analysis of levetiracetam, valproic acid, and phenytoin also found no statistically significant differences among the agents in terms of clinical seizure cessation, but there was a lack of statistical power to detect a difference.[17] Our review differs from past reviews in that only RCTs comparing levetiracetam with other agents were included (to minimize bias), along with the recently published study by Kapur and others.[15] However, our results are consistent with those of previous studies, in that no significant differences in SE cessation were found among the various AEDs.

Before publication of the large study by Kapur and others,[15] in 2019, comparative studies were each limited to a single centre, were underpowered, and lacked blinding. Furthermore, known regional variations in the common causes of SE and delays in treatment initiation (resulting in long duration of seizures before treatment) make it difficult to extrapolate the results of these earlier studies, which were based in South and West Asian countries, to Western populations. The addition of the multisite trial by Kapur and others[15] to this body of literature has provided confirmation of previous results, by means of an adequately powered study. In that study, AED administration occurred approximately 1 hour after the onset of seizure activity, patients of most age categories were included, and the etiologies represented local trends in North America.

The focus of the current systematic review was the treatment of SE in adults, and studies involving only pediatric patients were therefore excluded; however, most of the included trials involved children as well as adults. Three of the studies[11-13] included adolescents (at least 14 or 15 years old); however, the investigators did not report the number of

TABLE 2. Risk of Bias of the Included Studies

	Type of Bias; Level of Risk						
Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other
Chakravarthi et al. (2015)[11]	High	High	High	Unclear	Low	Low	Low
Mundlamuri et al. (2015)[12]	Low	Unclear	High	Unclear	High	Unclear	Low
Gujjar et al. (2017)[13]	High	Unclear	High	Unclear	Low	Low	Low
Nene et al. (2019)[14]	Low	Unclear	High	Unclear	Low	Low	Low
Kapur et al. (2019)[15]	Low	Low	Low	Low	Low	Low	Low

participants who were under 18, nor did they perform a subgroup analysis by age. Kapur and others[15] included patients as young as 2 years of age, and 39% of the participants were children or adolescents. In a subsequent publication from the same trial, the researchers did perform a subgroup analysis, which showed that results for the primary outcome of seizure cessation were consistent across age groups.[18]

All 5 studies included in the current review found no superiority of levetiracetam, phenytoin, or valproic acid for SE cessation. In addition, no differences were identified in terms of the need for ICU admission, the length of hospital or ICU stay, efficacy of the medications when administered as the second AED, neurologic function at hospital discharge, mortality, or adverse effects. However, there were signals that phenytoin may cause more hypotension and adverse cardiac effects, and that levetiracetam may cause more psychiatric adverse effects, such as agitation or psychosis.

Three of the included studies showed that in the case of failure of the first AED, giving a second antiepileptic agent increased the likelihood of seizure cessation, regardless of the order in which the medications were given.[12-14] Overall, the addition of a second AED, if needed, resulted in a total of 77% to 92% of patients experiencing seizure control. This benefit may prevent the need for intubation in some patients with SE.

There were differences among the trials in terms of the doses of AEDs given; in particular, the dose of levetiracetam ranged from 20 to 60 mg/kg (maximum 4500 mg).[11-15] In addition, differences in methodologies and definitions of the primary outcomes make it difficult to compare results across the various studies. Based on the available evidence, the ideal dose of levetiracetam for SE remains unclear, and there have not been any head-to-head trials comparing different levetiracetam doses for SE in adults.

With no proven difference among levetiracetam, phenytoin, and valproic acid in terms of efficacy for cessation of SE, other factors may dictate which AED to give after a benzodiazepine in patients with this condition. These factors may include the logistics of administration, drug cost, inclusion on hospital formularies, and drug availability. Valproic acid for IV administration is currently not marketed in Canada and is only available through Health Canada's Special Access Programme. Given its ease of preparation and rapid administration (it may be given as a 5-minute IV bolus "push" dose), valproic acid is a practical agent to administer between IV lorazepam doses.[19] Valproic acid is not commonly associated with hypotension, but potential cytochrome P450 interactions, metabolic disorder contraindications, and liver function must be considered before administration. Phenytoin has a number of potential issues that may make it a less desirable choice. Rapid administration of this drug, which is diluted in propylene glycol for solubility, has been associated with hypotension and cardiac arrhythmias.[20] It is therefore recommended to be given at a maximum rate of 50 mg/min, with 20–30 minutes often being required for administration of the complete dose.[20] This prolonged administration time may prevent the administration of other fluids and medications, including lorazepam, through the same IV line and could theoretically delay clinical onset of effect. Phenytoin can also cause local venous irritation during administration, which may be reduced by giving the dose through a large peripheral or central IV line. Fosphenytoin, the more costly water-soluble prodrug of phenytoin, is thought to be more readily tolerated and can be given at a faster infusion speed of 150 mg/min.[21] However, the faster infusion speed may not lead to a faster clinical onset because of the time required for metabolic activation (hydrolysis) into the drug's active form, and serious adverse effects also occur with fosphenytoin (as with phenytoin).[22-24] Phenytoin also requires careful therapeutic drug monitoring because of its narrow therapeutic window and nonlinear pharmacokinetics.[24] Finally, as an inducer of the cytochrome P450 3A4 and 2C9 isozymes, phenytoin is subject to many drug interactions.[20] In contrast, levetiracetam does not cause significant injection site irritation, can be administered over a shorter period (10–15 minutes), and does not have cytochrome P450–mediated drug interactions.[15,25] It has, however, been associated with neuropsychiatric effects, such as somnolence, ataxia, depression, and agitation.[25]

Some potential limitations of this systematic review are the small number of studies, the high risk of bias in some of the studies, and heterogeneity in terms of participants studied and definitions of SE cessation. Only 5 studies met the inclusion criteria for this review, and the number of participants in each trial ranged from 44 to 384. Only the largest trial, by Kapur and others,[15] reported a power calculation for their sample size. Exclusion of nonrandomized data from our review may have reduced the ability to detect trends in secondary outcomes (e.g., adverse effects) which may have been apparent with higher numbers of patients. Despite limiting this systematic review to RCTs, all of the included studies were ranked as having a high risk of bias in at least 1 domain, except for the trial by Kapur and others.[15] The most common reason for unclear or high risk of bias was the lack of blinding of study personnel or outcome assessors. Studies differed in terms of age of participants, definitions of SE, and definitions of SE cessation. This heterogeneity would make the use of a meta-analysis inappropriate for this review.

CONCLUSION

IV levetiracetam at doses of 20 to 60 mg/kg appeared to be just as effective as valproic acid 20 to 40 mg/kg or phenytoin 20 mg/kg when given with or after benzodiazepines for the treatment of SE. Levetiracetam efficacy rates for cessation of SE ranged between 46.9% and 81.8%, depending on the

definition used. Although perhaps underpowered to allow conclusive statements, the included studies showed no statistically significant differences among agents for secondary outcomes, including adverse effects. However, there were numerically more cases of hypotension and respiratory failure with phenytoin, and more cases of psychiatric adverse effects (e.g., post-ictal psychosis) with levetiracetam. Other factors, including drug interactions, comorbidities, logistics of administration, availability, and cost, may be considered on a patient-specific basis to determine the drug of first choice. Should a first antiepileptic agent fail to control SE, the addition of a different AED treatment may increase the likelihood of achieving cessation of SE.

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Gestion des approvisionnements en médicaments pendant la pandémie de COVID-19 : expérience québécoise en établissement de santé

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INTRODUCTION

Le premier cas de COVID-19 au Canada a été signalé en Ontario le 25 janvier 2020. L'Organisation mondiale de la santé a déclaré l'état de pandémie à la COVID-19 le 11 mars 2020[1]. Un état d'urgence sanitaire a été déclaré par le Gouvernement du Québec le 13 mars 2020[2]. Considérant l'effet de la pandémie sur l'économie et sur les soins de santé, des pénuries de médicaments ont été prévues au Canada[3,4]. Deux réserves COVID ont été établies. L'objectif de cet article est de décrire la gestion de l'approvisionnement en médicaments hospitaliers durant la pandémie à la COVID-19.

DESCRIPTION DE LA PRATIQUE

Cellule de crise

Une cellule de crise composée de six chefs de département de pharmacie du Québec a été formée, épaulée par deux pharmaciennes-conseils, des membres du personnel des groupes d'approvisionnement en commun (GAC) et des représentants du ministère de la Santé et des Services Sociaux (MSSS). Deux chefs de département de pharmacie par GAC ont été recensés pour la cellule de crise, soit le président et le vice-président de chaque comité de pharmaciens des GAC. Peu importe leur établissement de santé, chaque chef assure la représentation de toutes les missions de soins du réseau de la santé. Au Québec, les établissements de santé regroupent le plus souvent toutes les missions (c.-à-d. centre hospitalier, centre hospitalier de soins de longue durée (CHSLD), centre de réadaptation, centre jeunesse et centre local de services communautaires (CLSC)). Afin de faire face à la pandémie, de nombreuses actions ont été entreprises et coordonnées par cette cellule. L'annexe 1, disponible à l'adresse https://www.cjhp-online.ca/index.php/cjhp/issue/view/207 présente un fil chronologique des principaux événements liés à la gestion des stocks de médicaments durant la pandémie.

Liste de médicaments critiques

Une liste de 220 médicaments critiques (57 dénominations, 220 présentations commerciales) a été établie en consultant les principaux chefs de département de pharmacie et leur équipe clinique. Cette liste, qui regroupe les médicaments jugés essentiels pour faire face à la pandémie de COVID-19, a servi de base à plusieurs actions entourant la gestion des stocks. Des ajouts ont été portés à la liste en cours de pandémie, notamment pour tenir compte des besoins en soins palliatifs. L'annexe 2, disponible à l'adresse https://www.cjhp-online.ca/index.php/cjhp/issue/view/207 présente la liste de médicaments critiques en vigueur au 13 avril 2021.

Organisation de rencontres avec les parties prenantes

Dès le début de la pandémie, un arrimage s'est établi avec la direction des affaires pharmaceutiques du MSSS, et des rencontres ont été organisées avec les fabricants de médicaments et les grossistes. Ces rencontres nous ont permis de quantifier nos besoins en médicaments et ont donné l'occasion à l'industrie pharmaceutique de réviser les priorités de production et de s'assurer de la disponibilité de plusieurs médicaments critiques en soins intensifs, en médecine et en soins de fin de vie (p. ex. curares, opiacés, anticholinergiques).

Gestion des communications et des suivis

Un plan de communication a été établi et ajusté sur une base régulière. Trois forums principaux ont été mis en place ou utilisés aux fins de gestion des enjeux liés à la pandémie, soit 1) la cellule de crise décrite avec le MSSS, 2) un comité MSSS-parties prenantes en pharmacie formé de l'ordre professionnel, des associations professionnelles et des GAC et 3) un comité centre d'acquisitions gouvernementales (CAG)-distributeurs pharmaceutiques. En plus de la cellule de crise, l'information était partagée et discutée avec l'ensemble des chefs de département de pharmacie du Québec

sur une base hebdomadaire. Des rencontres fréquentes ont été établies sur Zoom puis sur Microsoft Teams. Des équipes et des canaux de communication précis ont été créés afin de partager des fichiers de travail (p. ex. suivi des inventaires, partage de stocks à courte péremption, scénarios) et un tableau de bord pour le suivi.

Simulation dynamique des besoins en médicaments

Afin de quantifier les besoins en médicaments à l'échelle du Québec, une simulation dynamique des besoins en médicaments a été mise en place par la cellule de crise. La simulation a été conçue en tenant compte de la liste de médicaments critiques, du taux d'utilisation de chaque médicament par patient admis en soins intensifs ou en soins palliatifs, d'une posologie moyenne journalière par médicament par patient et d'une courbe de jours-présences en soins intensifs et en soins palliatifs. La simulation a été ajustée au fur et à mesure en tenant compte des données réelles cumulées.

Périodiquement, des pharmaciens de soins intensifs et de soins palliatifs de plusieurs établissements touchés ont été sondés afin de commenter les paramètres des scénarios et de s'assurer de l'adéquation de la simulation avec les pratiques évolutives sur le terrain.

Des travaux préliminaires ont été nécessaires afin de mettre en place cette simulation dans un chiffrier complexe relié à plusieurs fichiers sources. Dans un premier temps, nous avons extrait l'ensemble des ventes de médicaments aux départements de pharmacie par dénomination commune internationale (DCI) pour tout le Québec afin d'établir la dose quotidienne utilisée par le réseau de la santé. Cette démarche a permis d'établir le besoin de base du Québec par DCI. Dans un deuxième temps, nous avons conçu une matrice de tous les besoins exprimés par les chefs de département de pharmacie (c.-à-d. commande ferme pour la réserve nº 1) et avons converti cette information en mg requis par DCI. Dans un troisième temps, à partir des données de sondages périodiques, nous avons simulé les besoins de patients en soins intensifs, en médecine générale et en soins palliatifs en tenant compte d'une sélection de médicaments applicable à chaque clientèle. Dans un quatrième temps, nous avons intégré les données de projection du nombre quotidien de patients dans ces trois secteurs. Ces courbes ont été révisées périodiquement en tenant compte de données partagées par le MSSS ainsi que du nombre réel de patients atteints de la COVID dans ces secteurs. Toutes ces données ont permis d'établir un modèle permettant de vérifier si les stocks en place (c.-à-d. à l'échelle locale et chez les grossistes) allaient s'avérer suffisants pour répondre aux besoins pour une période déterminée.

Rehaussement des seuils d'inventaire en établissement de santé

Depuis plusieurs années, les chefs de département de pharmacie du Québec réclament une hausse du nombre moyen de jours d'inventaire des médicaments et des espaces additionnels d'entreposage, sachant qu'il leur revient d'établir la sélection des médicaments et d'assurer la disponibilité des médicaments requis aux usagers en dépit des ruptures de stock fréquentes chez les fabricants[5]. En réaction à cette demande, le sous-ministre de la santé écrivait aux présidents-directeurs généraux des établissements de santé du Québec en 2017 que des « inventaires inférieurs à quatre semaines devraient généralement être évités »[6]. Dès le début de la pandémie, les pharmaciens de la cellule de crise ont demandé au MSSS que ce nombre de jours soit officiellement rehaussé à l'échelle du réseau. En juin 2020, une nouvelle missive du MSSS demandait « de détenir des inventaires de 60 jours pour la majorité des produits d'usage courant et de 90 jours pour les produits critiques »[7]. Ces deux interventions concertées ont contribué à rendre les établissements de santé moins vulnérables aux problèmes d'approvisionnement en médicaments.

Développement d'un outil de surveillance des inventaires

Afin d'atteindre les niveaux d'inventaire ciblés, chaque chef de département de pharmacie de tous les établissements du Québec devait mettre à jour, sur une base quotidienne pour commencer, puis hebdomadaire, un chiffrier comportant une sélection des médicaments critiques (figure 1). Cet outil de surveillance a permis non seulement de quantifier les inventaires mais également de vérifier le nombre de jours d'autonomie en tenant compte des volumes d'activités réels et prévus. De plus, une analyse hebdomadaire et consolidée de ces données était transmise au MSSS afin d'informer les autorités de la capacité des établissements à faire face à la pandémie.

Réserves ministérielles

En vertu d'un arrêté ministériel, deux réserves de médicaments successives ont été établies[8]. Une première réserve a été constituée à partir des données de simulation et d'une commande ferme de médicaments critiques par chaque chef de département de pharmacie pour la période du 1er mai au 30 août 2020. Une commande ferme signifie que les médicaments périmés ne peuvent être retournés et ne sont pas admissibles à une demande de crédit auprès du grossiste ou du fabricant. Une seconde réserve a été constituée à partir des données révisées de la simulation et d'une commande ferme du MSSS pour la période du 1er septembre 2020 au 30 juin 2021. Dans les deux cas, les grossistes à forfait (McKesson, McMahon) ont été mis à contribution en convenant de modalités de fonctionnement. En sus de ces deux réserves conservées chez les deux distributeurs à forfait avec le CAG, une réserve ministérielle de solutés a été mise en place et les niveaux d'inventaires des solutés par établissement ont été rehaussés à raison de 60 ou 90 jours selon le type de soluté.

Outil de partage des stocks de médicaments

Il est difficile d'estimer avec précision les besoins en médicaments. Bien que la simulation nous ait permis d'établir une zone de confort en matière de disponibilité de certains médicaments, il s'est avéré nécessaire de mettre en place un système pour minimiser les pertes. Un chiffrier de partage sur Teams (Microsoft, Seattle, WA, É.-U.) a été créé pour faciliter les échanges entre les établissements. Les partages s'effectuent directement entre les établissements, après contact téléphonique ou par courriel de la part du personnel de gestion des stocks du département de pharmacie de chaque établissement au moyen d'un envoi personnalisé.

Changements de pratique

La cellule de crise a recensé, proposé et examiné de nombreuses actions afin d'optimiser la disponibilité des stocks de médicaments. En collaboration avec l'Institut national d'excellence en santé et services sociaux (INESSS), elle a produit des outils permettant de faciliter l'interchangeabilité de certains médicaments. Par exemple, on a proposé de changer certaines pratiques (cisatracurium ou rocuronium), d'éviter les préparations faites à l'avance, de favoriser la voie orale, de fractionner les volumes de certains formats de préparation pour éviter les pertes lors d'un arrêt de thérapie, de prolonger la date limite d'utilisation de préparations ou de tubulures en situation critique ou encore de recourir à différentes possibilités thérapeutiques.

ÉVALUATION ET PERSPECTIVES

En dépit du nombre élevé d'hospitalisations liées aux deux vagues d'infections à la COVID-19, il n'y a pas eu de pénuries avérées de médicaments dans les hôpitaux du Québec compte tenu de l'approche mise en place, de la proactivité et de la très grande collaboration des pharmaciens en établissement de santé. Les réserves accumulées nous ont même permis de venir en aide à d'autres provinces du Canada qui étaient aux prises avec des difficultés d'approvisionnement. Avec la mise en place de la 2e réserve, nous n'anticipons pas de pénuries de médicaments d'ici décembre 2021. Les travaux se poursuivent en tenant compte de l'évolution de la pandémie afin d'anticiper les besoins et les actions visant à assurer un approvisionnement adéquat.

La mise en place de la cellule de crise a été effectuée avec succès, grâce à la collaboration de tous, incluant les équipes des trois GAC en place au Québec (SigmaSanté et les deux groupes couvrant l'Est et l'Ouest du Québec). Bien avant la pandémie, le Gouvernement du Québec avait planifié la fusion des trois GAC au sein d'un nouveau Centre d'acquisitions gouvernementales[9]. Ce changement législatif et organisationnel a été effectué le 1er septembre 2020, et la cellule de crise mise en place fait office de nouveau comité de gouvernance représentant les pharmaciens des trois GAC fusionnés au sein du nouveau centre. Cette cellule sera pérennisée au terme de la pandémie.

CONCLUSION

Le Québec a été touché de façon importante dès le début de la première vague, et des mesures sanitaires ont été mises en place rapidement en pharmacie en tenant compte de l'évolution de la pandémie[10]. Les chefs de département de pharmacie, soutenus par le personnel des GAC, ont été proactifs, créatifs, solidaires et efficaces, ce qui leur a permis d'éviter des pénuries de médicaments et d'assurer une prestation sécuritaire de services et de soins pharmaceutiques à la population québécoise.

Cette crise sans précédent met en évidence la nécessité de pérenniser une approche agile et proactive de gestion des médicaments ainsi que certains outils mis en place afin de faire face à de nouvelles crises (p. ex. autre pandémie, conflit commercial avec un pays étranger, pénurie soutenue de plusieurs produits). Indépendamment de la pandémie, la mise en place du CAG et d'un comité des pharmaciens forts et structurés, avec présence d'une équipe de pharmaciens-conseils, est une occasion d'accroître la collaboration entre

				DATE				CASE 1 % de reprise des activités usuelles	100%
				2021-04-07				CASE 2 Prévision nombre de patients USI COVID	150
Générique	Format	Dose quotidienne moyenne par patient COVID (80kg)	% de patient COVID susceptibles de recevoir cette thérapie	Inventaire (format)	Quantité totale en inventaire (mg ou mcg)	Consommation de base POUR 30 JOURS (mg ou mcg)	Consommation de base par 24h selon le facteur de reprise des activités (mg ou mcg)	Consommation COVID par 24h selon le nombre de patients COVID (mg ou mcg)	Nombre de jours d'autonomie avec les inventaires disponibles en fonction des consommations prévues (base + COVID)
Médicaments de soins critiques									
Total cisatracurium	2 mg/mL, 10 mL	345	19%	41232	824640	43208	1440	9833	73,2
Total rocuronium	10 mg/mL, 5 mL	1000	19%	91186	4559300	1351562	45052	28500	62,0
Fentanyl	50 mcg/mL, 2 mL			155062	15506200				
	50 mcg/mL, 5 mL			61309	15327250				
	50 mcg/mL, 10 mL			22021	11010500				
	50 mcg/mL, 20 mL			15837	15837000				
	50 mcg/mL, 50 mL (fiole)			2104	5260000				
Total fentanyl		4120	49%		62940950	15083219	502774	302820	78,1
	10 mg/mL, 1 mL			181649	1816490				

FIGURE 1. Extrait d'un fichier type de l'outil de surveillance de l'inventaire et un profil synthèse de l'état des stocks au Québec. Le tableau intégral est présenté à l'annexe 3, disponible à l'adresse https://www.cjhp-online.ca/index.php/cjhp/issue/view/207.

tous les chefs de département de pharmacie du Québec afin d'optimiser la gestion des stocks sans limiter les occasions d'affaire pour le marché pharmaceutique (c.-à-d. en préservant les cycles contractuels régionaux en place).

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When No Treatment Is the Treatment: Mental Illness–Related Case Report

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INTRODUCTION

Reaching a diagnosis is often difficult, involving multiple steps. According to Balogh and others,[1] mental health diagnoses in particular are challenging, especially in terms of distinguishing between physical and mental health problems. Sometimes, physical conditions manifest as psychiatric ones, and vice versa.[2,3] Furthermore, there are concerns about missing psychiatric diagnoses and potential problems with overtreatment, as seen in prescribing cascades.[4] Indeed, diagnosis is an inferential process, with conclusions that may change over time and that may include misdiagnoses. This case report highlights how a patient with a complex presentation was incorrectly given a diagnosis of severe mental illness and treated accordingly for more than a decade before the deprescribing of unnecessary medications provided new insights into the correct diagnosis.

CASE REPORT

A 56-year-old married man was referred to the electroconvulsive treatment (ECT) department.* However, the referral was deferred because the patient's extensive list of pharmaceuticals included many mood stabilizers that were incompatible with ECT. Before proceeding further with the planned ECT, the patient was transferred to the Psychosis Coordinated Care Service (PCCS) of the Centre for Addiction and Mental Health (Toronto, Ontario) for clarification of the diagnosis, as well as review and optimization of his pharmaceutical treatment.

During the first meeting at the PCCS, the patient stated his current inability to function properly. The patient had worked for 28 years on the assembly line of a motor vehicle company and had taken medical leave after a myocardial infarction. He was last employed at the company 7 or 8 years before the current presentation. He reported it was hurtful "being told I wasn't good enough to go back to work." He also reported, "I've always been a bit of a worrier but never to this extent." Indeed, after the myocardial infarction, he was forcing himself to do daily activities.

On assessment, the patient had poor eye contact. He was sedated and fell asleep on several occasions. He described his mood as low. He stated that he felt tired and reported insomnia, despite taking 5 medications to help with sleep. He also felt that people were watching him: they "stare at me." He reported auditory hallucinations (not commanding), telling him what he should and should not do—mostly instructing him not to leave his house, to be more careful, and so on. Overall, the patient found his situation disturbing and upsetting.

When questioned about his understanding of his diagnosis, the patient reported misunderstanding. He indicated that he had searched for and found information about schizoaffective disorder, which apparently listed "all my symptoms". He therefore assumed that he "had that or something close to that". He reported his appreciation of the role of medications and the risks of stopping them. There were no adherence issues.

Apart from the excessive sedation, the patient's symptoms had not remitted over the years, despite the overabundance of prescribed medications.

The patient's illness was notable for symptoms of depression and anxiety that seemed to have commenced 6 to 9 months after his father died of heart disease. Apparently, his father's death was traumatic to the patient, and he turned to alcohol. In 2010, the patient himself had a myocardial infarction, followed a year later by a motor vehicle crash while he was intoxicated. This event was, as he described it, a wake-up call, and he stopped drinking. Upon admission to the PCCS, there were no reports of substance use apart from nicotine dependence and caffeinism.

The patient's medical and psychiatric problems requiring hospitalization and treatment had started about a decade before the current presentation, after the myocardial infarction. In terms of medical treatment, it appeared that the usual medications known to reduce cardiovascular risk

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

after myocardial infarction, such as angiotensin-converting enzyme inhibitors, statins, β-blockers, and acetylsalicylic acid,[5] were prescribed. In addition, the proton pump inhibitor (PPI) pantoprazole, for treatment of gastroesophageal reflux disease, had been part of the patient's regimen since 2009. The patient was also being treated for diabetes. In terms of psychiatric treatment, the patient was taking a large number of psychotropic agents, as discussed further below.

The PCCS treatment team suspected the occurrence of prescribing cascades,[4] a type of polypharmacy that occurs when an adverse drug event is misinterpreted as a new medical condition, and a second medication is prescribed. With the involvement of the patient, his wife, and an interdisciplinary team (psychiatry, pharmacy, and nursing), a clinical process map was applied and a deprescribing treatment plan was created. The patient and his wife were in full agreement with the plan. Both were motivated and wanted the removal of unnecessary medications. With the patient's consent, the PCCS team contacted his primary care provider, who had been prescribing all the medications, and his community pharmacy and informed them that the PCCS team would take over prescribing to ensure coordination of care and appropriate monitoring. All of the parties agreed. Weekly meetings were scheduled for psychiatric evaluation and close monitoring during the planned 6-month deprescribing period. A safety plan was also put in place to allow for inpatient admission in case of deterioration in the patient's mental state.

The goal was to eliminate unnecessary medications, improve safety, and permit a clearer diagnosis, thus improving the patient's quality of life.

DISCUSSION

Whereas polypharmacy is generally defined as the routine use of 5 or more medications,[6] psychiatric polypharmacy involves the concurrent use of 2 or more psychiatric medications.[7,8] The occurrence of polypharmacy does not necessarily denote the inappropriate or incorrect use of medications; however, in this patient's case, the medication regimen appeared to confer more risks than benefits. This situation led to the reconsideration of treatment through a deprescribing approach.

This patient's psychiatric regimen involved a plethora of drugs for which indications, times of initiation, and intended duration were unclear. Indeed, over the years he had been given various diagnoses related to psychotic and mood symptoms, such as depression, bipolar disorder – depressive type, bipolar I disorder with psychotic features, schizophrenia, and most recently schizoaffective disorder – bipolar type. In fact, the ECT referral had been intended to improve the patient's mental state, given his continuing symptoms and lack of response to the numerous pharmaceuticals in his regimen (listed in Table 1).

The patient had 2 psychiatric hospitalizations (in 2012 and 2013) for apparent depression with suicidal ideation. As previously noted, there may be an evolution of diagnoses over time, especially in mental health. In this case, the patient's depression might have been related to his myocardial infarction, ongoing grief after his father's death, or nonpsychiatric drugs that induce negative psychological adverse effects. Additionally, the suicidal ideation could have been an adverse effect related to his prescribed medications. In any event, there had been several trials of antidepressants and anxiolytics over the previous decade without persistent improvement in symptoms. This situation prompted the referral for ECT and recommendations for future changes in therapy, such as augmentation with the antipsychotic lurasidone or initiation of clozapine for treatment-resistant schizophrenia.

Evidently, the patient's polypharmacy was an obstacle to clear diagnosis, given the presence of too many confounding factors. Deprescribing was needed because the risk of interactions with other medications or conditions and the risk of cumulative harms outweighed any potential benefits.

The medications were tapered and discontinued in an orderly fashion, starting with 2 medical agents, pantoprazole and propranolol, that were deemed unlikely to be necessary at the time of consultation. Indeed, given their known psychiatric side effects, they were most likely confounding other therapies. For instance, the long-term use of PPIs (i.e., longer than 1 year) may result in serious medical adverse events[9] and psychiatric symptoms such as depression, agitation, confusion, and disorientation. Other psychotic problems associated with PPIs include auditory and visual hallucinations.[10,11] The pantoprazole had been initiated in 2009 (a decade before), around the same time the myocardial infarction was diagnosed. The PCCS team questioned whether this agent had been prescribed because of confusion about the patient's symptoms. The product monograph for pantoprazole[12] further reports potential adverse effects of nervousness, tremor, sleep disorders, hyperlipidemias and lipid increases (triglycerides, cholesterol), depression (and associated aggravations), and disorientation (and associated aggravations). The agent was deemed inappropriate, and was therefore tapered and discontinued.

A similar rationale was applied for the β-blocker propranolol. Although it is common for a β-blocker to be prescribed after myocardial infarction,[5] the dose appeared incongruent (too low) for this purpose. Additionally, propranolol had been introduced in 2016, approximately 5 years after the infarction. The reason for its use remained nebulous (although arrhythmia or akathisia was surmised). Notably, propranolol has psychiatric adverse effects that include visual hallucinations, auditory hallucinations, depression, and paranoid psychosis.[13-15] These adverse reactions have all diminished in this patient after withdrawal of the drug.

Furthermore, because propranolol has β-adrenergic blocking activity, it may block premonitory signs and

TABLE 1. Patient's List of Medications

Medications before Deprescribing	Suspected Diagnoses and Date of Initiation	Medications after Deprescribing
Acetylsalicylic acid 81 mg qAM	Post–myocardial infarction; about 2010	Acetylsalicylic acid 81 mg qAM
Asenapine 5 mg S/L qHS	Trial of new antipsychotic medication; about 2019	—
Atorvastatin 80 mg once daily	Post–myocardial infarction; about 2010	Atorvastatin 80 mg once daily
Canagliflozin 100 mg qAM	Diabetes inferred; date of initiation unknown	Canagliflozin 100 mg qAM
Clonazepam 0.25 mg BID + clonazepam 0.5 mg qHS + clonazepam 0.25 mg every other day PRN (per community pharmacy, taken regularly by patient)	Anxiety; date of initiation unknown	—
Lamotrigine 300 mg once daily	Mood stabilizer; date of initiation unknown	—
Lithium 450 mg BID	Mood stabilizer; date of initiation unknown	—
Metformin 500 mg BID	Diabetes inferred; date of initiation unknown	Metformin 500 mg BID
Multivitamin with minerals once daily	Supplement; date of initiation unknown	Multivitamin with minerals once daily
Nitroglycerin 0.4 mg PRN for chest pain	Post–myocardial infarction; about 2010	Nitroglycerin 0.4 mg PRN for chest pain
Pantoprazole sodium 40 mg once daily	Possible GERD; about 2009	—
Pregabalin 150 mg once daily	Anxiety; date of initiation unknown	—
Propranolol 10 mg TID	Diagnosis unknown; date of initiation unknown	—
Ramipril 10 mg once daily	Post–myocardial infarction; about 2010	Ramipril 10 mg once daily
Risperidone 4 mg once daily	Trial of new antipsychotic medication; about 2020	—
Venlafaxine 112.5 mg once daily	Anxiety and depression; date of initiation unknown	—
Zopiclone 7.5 mg qHS and during the day if required (per community pharmacy, taken regularly by patient)	Insomnia; date of initiation unknown	—
Agents added temporarily during PCCS admission to support sleep		—
Quetiapine, up to 75 mg qHS	Sleep optimization; about 2020	
Olanzapine, up to 15 mg qHS	Trial of new antipsychotic medication; about 2020	

BID = twice daily, GERD = gastroesophageal reflux disease, PCCS = Psychosis Coordinated Care Service, PRN = as needed, qAM = in the morning, qHS = at bedtime, S/L = sublingual, TID = 3 times daily.

symptoms (such as changes in pulse rate and blood pressure) of acute hypoglycemia, a condition that may contribute to mood fluctuations. In this patient, unrecognized hypoglycemia might have been caused or exacerbated by the hypoglycemic agents he was taking. The propranolol was also discontinued.

The same systematic approach, based on clinical experience, judgment, and evidence, guided the deprescribing process for each medication as listed in Table 1. We are of the opinion that the deprescribing process was successful. At the time of writing, the patient was doing well. The ECT was deemed unnecessary, and the referral was therefore cancelled.

CONCLUSION

Although polypharmacy can be appropriate if thoughtfully applied, it is often harmful. In fact, it is possible that this patient's diabetes was a metabolic side effect related to past use of antipsychotics. Moreover, there is little evidence that polypharmacy enhances clinical outcomes.[8] In this case, all psychotropics were ceased with no adverse consequences for the patient. This case report illustrates the adage that sometimes "less is more". Minimizing prescribing cascades[4] and deprescribing when appropriate can be powerful tools to clarify diagnoses and improve safety and patient outcomes. The 6-month period of deprescribing for this patient highlighted the necessity for ongoing medication review and management by both prescribers and dispensers and led us to the conclusion that the patient did not have a severe mental illness.

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To Go Far, Go Together

Zack Dumont

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The proverb itself has stood the test of time: If you want to go fast, go alone; if you want to go far, go together. The adage is not clearly attributed to any one person, and perhaps this is intentional. It speaks to what leadership isn't, and in place beckons collaboration, cooperation, coordination, and engagement, tools leaders strive to use.

Leadership is about others. An individual's specific credentials or qualifications do not guarantee success. A leader must find ways to create a particular environment; one where the collective competency of team members can optimally radiate. Further, when presented with an opportunity to lead, we learn that the spotlight will come—there are times when this will be welcome and others when it won't—thus, there's no need to force it. Instead, the opportunity can be used to shine the spotlight on others.

Leadership is about listening to others. It's not about the leader getting first crack. To lean on another important saying: leaders eat last. It's still great for a leader to bring forth ideas, especially if they are innovative. However, an idea is not much good if the visionary can't help others see how the benefits may outweigh the risks. While we must work together to ensure we're attentive to every voice, it's up to those in leadership roles to communicate their vision in compelling and inspirational ways. This helps reach the state whereby a team can make informed decisions. On that note, it's not all about 'majority rule'. It's about first seeking consensus.

Leadership is about *all* time. For example, we mustn't simply aim to balance this year's budget, we must also aim to balance next year's, and the year after that, and so on. It's about setting-up to have infinite budget cycles. It's critical not to throw away everything for today, as tomorrow is just as important, and vice versa. On this, we should seek balance. To go completely without today in speculation for tomorrow is not only unpopular, but arguably unethical. As leaders, we must think about sustainability, consider both today and tomorrow, and balance making safe decisions with taking calculated risks. A legacy isn't about what is done for the current state, it's about what is left behind for those who come next.

In these times of unfamiliar adversity and uncertainty, I've never been more grateful for and optimistic about the Canadian Society of Hospital Pharmacists (CSHP). Despite attending more virtual meetings than we could've ever possibly imagined, battling tumultuous economics, and having the odds stacked against us, our Board and Executive have risen to the challenge. To all CSHP members and supporters, staff, and volunteers, including those on affiliated boards, branches, committees, and task forces, you likely signed up for something very different than what you got. Yet, the show goes on! This is possible, because you are all leaders—you make it about others, about their wants and needs—CSHP continues to succeed, and the future is bright. We're sticking together, and we're going the distance.

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Si on veut aller loin, il faut partir ensemble

par Zack Dumont

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Le proverbe a résisté à l'épreuve du temps : « Si vous voulez aller vite, partez seul. Si vous voulez aller loin, partons ensemble. » L'adage n'est pas attribué à une personne en particulier et c'est peut-être intentionnel. Il illustre ce que le leadership n'est pas et, au lieu de cela, il invite à la collaboration, à la coopération, à la coordination et à l'engagement; en un mot, des outils que les leaders s'efforcent d'utiliser.

Le leadership se rapporte aux autres. Les titres ou les diplômes ne sont pas les garants de la réussite. Un leader doit trouver des moyens de créer un environnement particulier; un environnement où la compétence collective de tous les membres de l'équipe peut rayonner de manière optimale. De plus, lorsque l'occasion de mener se présente, nous apprenons que nous serons éventuellement sous le feu des projecteurs – ce sera parfois bien accueilli, et parfois non – inutile de forcer, donc. Ainsi, on peut plutôt utiliser cette occasion pour braquer les projecteurs sur les autres.

Le leadership, c'est savoir écouter les autres, et pas nécessairement donner le premier coup de pioche. Pour s'appuyer sur un autre dicton important : les leaders mangent en dernier. Pour un leader, c'est certainement bien de proposer des idées, surtout si elles sont innovantes. Cependant, une idée ne vaut pas grand-chose si le visionnaire ne peut aider les autres à voir comment ses avantages l'emportent sur les risques. Bien qu'il faille travailler ensemble pour que chaque voix soit prise en compte, la communication de la vision d'une manière convaincante et inspirante relève des personnes qui occupent des postes de direction. Cela permet d'atteindre l'état dans lequel une équipe peut prendre des décisions éclairées, ce qui ne se résume pas seulement à « la majorité l'emporte » : il s'agit d'abord de trouver un consensus.

Le leadership demande qu'on voie loin. Par exemple, il ne s'agit pas seulement d'équilibrer le budget de cette année, il faut aussi équilibrer celui de l'année prochaine, celui de l'année d'après, et ainsi de suite. Il s'agit de mettre en place des cycles budgétaires… à l'infini. Il ne faut surtout pas tout dépenser maintenant, car demain se prépare aujourd'hui et aujourd'hui est le fruit d'hier. Pour cela, il nous faut marcher sur un fil. Faire fi d'aujourd'hui et parier sur demain est non seulement mal vu, mais aussi, sans doute, contraire à l'éthique. En tant que leaders, nous devons penser à la durabilité, prendre en compte aujourd'hui et demain, et trouver l'équilibre entre les décisions sûres et les risques calculés. Un héritage ne se laisse pas à la génération actuelle, mais à celles qui viendront ensuite.

En ces temps difficiles marqués par des incertitudes, je n'ai jamais été aussi reconnaissant et optimiste envers la Société canadienne des pharmaciens d'hôpitaux (SCPH). Bien que nous ayons assisté à plus de réunions virtuelles que nous n'aurions pu l'imaginer, que nous ayons lutté contre une économie tumultueuse et que toutes les chances aient été contre nous, notre conseil d'administration et notre équipe de direction ont relevé le défi. À tous les membres et sympathisants de la SCPH, le personnel et les bénévoles, y compris les membres des conseils, sections, comités et groupes de travail affiliés, vous vous attendiez probablement à une expérience quelque peu différente de celle que vous avez vécue. Pourtant, nous continuons! C'est possible, parce que vous êtes tous des leaders. Vous faites le nécessaire pour les autres, leurs désirs et leurs besoins. La SCPH engrange les succès et l'avenir est prometteur. On se serre les coudes et on va plus loin.

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