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Opioid Stewardship: Moving Beyond the "Why" to the "How"

Glen Brown

The devastation imposed on Canadians' lives by the consequences of inappropriate, excessive, or unquantified opioids has been well described and well publicized in recent years. These detrimental consequences of opioids across multiple facets of society have forced all stakeholders to examine their practices in the provision of opioids to Canadians, including those individuals with an obvious need for adequate analgesia. The Canadian Society of Hospital Pharmacists (CSHP) has responded to the challenge of the opioid crisis by engaging its members in reflection and action on methods by which Canadian hospital pharmacists can contribute to minimizing the potential for inadvertent or inappropriate opioid access. A previous editorial in the *Canadian Journal of Hospital Pharmacy* (*CJHP*) highlighted the need for Canadian hospitals, and their associated pharmacy departments, to scrutinize their opioid-handling processes and resolve weaknesses that could facilitate drug diversion, and described potential mechanisms for doing so.[1] CSHP has produced a 47-page guideline to assist pharmacy departments in securing the drug distribution network.[2] Now, the challenge lies in optimizing opioid therapy for the treatment of pain in individual patients, both within and beyond our institutions. How can we identify the individual patients, the populations of patients, and the settings where opioid use is inappropriate, excessive, or ripe for opioid diversion?

Such a review of opioid stewardship practices within individual institutions may seem like a daunting task, but resources are becoming available to assist in identifying patients at risk. Elsewhere in this issue of *CJHP*, Woods and others[3] describe development of a tool to identify patients within various care areas of the hospital who would be at risk of adverse outcomes from opioids. They report that practising pharmacists found the tool—which described risk factors for adverse outcomes from opioids and corresponding potential interventions to minimize risk—useful but potentially challenging to incorporate into their daily practice.[3] Hopefully, these investigators will assess the impact of this tool on opioid use within their institution and share their findings in a future article. This is but one example of the tools and other resources that are now available for establishing or enhancing an opioid stewardship program.

For maximum impact from stewardship initiatives, institution-wide or health system–wide coordination of key clinicians, administrators, and quality assessment personnel is required. Two recently published articles provide thorough discussions, with examples, of the administrative structure, involved disciplines, and recommended tasks for achieving the desired change in the culture of opioid use in a health care setting.[4,5] Pharmacists should not, and cannot, face the challenge of opioid stewardship alone; rather, we should utilize our expertise in pain management, drug therapy optimization, and education of clinicians and patients to assist the whole care community in the use of opioids. The authors of these 2 articles suggest that any stewardship program should, where possible, explore and adopt methods for using non-opioids as first-line analgesics, and establish processes (for drug selection, dosages, durations, routes, and discontinuation) for optimum use of any opioid therapy that is deemed essential.[4,5]

Strategies for using non-opioids for initial treatment of pain require agreement from all disciplines involved in the care of patients experiencing various painful conditions. Pharmacists can participate in, and potentially lead, the review of indications for and efficacy of non-opioids for the treatment of specific conditions. Through their evaluation of the published literature and their skillful provision of education, pharmacists are key contributors in achieving consensus among clinicians regarding the utility and efficacy of non-opioid treatment.

Pharmacists can also be key contributors in identifying methods to minimize the exposure of individual patients to opioids during their interactions with health care institutions. Such processes could involve utilizing the pharmacy distribution system to identify patients who are receiving more than one opioid by the same route at the same time. For inpatients,

limiting the magnitude of dosage ranges, limiting initiation of parenteral administration to specific scenarios, and enhancing vigilance in administration of long-acting opioid formulations (patches or sustained-release oral dosage formulations) are examples of processes that pharmacists could undertake to reduce the risk associated with any obligatory opioid use.[6] Alternatively, a pharmacist's review of the quantity of opioid provided upon discharge may identify opportunities to reduce opioid exposure, although this approach has not been successful in all settings.[7] A group of pharmacists in Minneapolis, Minnesota, have published a thorough description of the expectations for review of all opioid treatments by pharmacists within their institutions,[6] which can serve as a good starting point for Canadian pharmacists wishing to establish realistic expectations of engagement.

Pharmacists can also influence opioid use through educational activities for providers and patients. Researchers from London, Ontario, demonstrated that education of clinicians and patients, in conjunction with established analgesic strategies, can reduce opioid requirements after various types of surgery.[8,9] Pharmacists' educational offerings could cover the topics of pain assessment, treatment regimens, and safe storage and disposal of narcotics.[4] Education of patients about the appropriate outpatient use of naloxone and instruction in methods to identify and resolve symptoms of opioid withdrawal are additional areas that could benefit from pharmacists' expertise.[5]

The need for intervention is great, and the diversity of interventions is wide. Now is the time for pharmacy departments and individual pharmacists to encourage their care communities (hospitals or heath care networks) to establish and implement effective strategies for opioid stewardship. Once launched, such initiatives are doomed to fail unless processes are established for the ongoing measurement and evaluation of the impact of these efforts on opioid use.[7] Clinicians from Houston, Texas, recently published their recommendations, along with some commentary by other clinicians, for 19 quality indicators that would be useful in measuring the ongoing, sustained effects of opioid stewardship activities.[10] All Canadian institutional pharmacists are encouraged to move from discussion of potential benefits to implementation of actions to optimize the use of opioids for their patients. In lay terms, it's time for "the rubber to hit the road". As you gain experience in this area, please measure your successes and failures, and tell others about your techniques so that we can all learn the "how" of opioid stewardship.

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Intendance des opioïdes : Passer du « pourquoi » au « comment »

par Glen Brown

Les conséquences désastreuses imposées à la vie des Canadiens par l'administration inappropriée, excessive ou non quantifiée d'opioïdes ont été bien décrites et bien médiatisées au cours de ces dernières années. Ces conséquences préjudiciables dans de multiples facettes de la société ont poussé les parties prenantes à examiner leurs pratiques en matière de délivrance des opioïdes aux Canadiens, y compris à ceux ayant manifestement besoin d'une analgésie adéquate. La Société canadienne des pharmaciens d'hôpitaux (SCPH) a relevé le défi posé par la crise des opioïdes en invitant ses membres à réfléchir aux méthodes par lesquelles les pharmaciens d'hôpitaux canadiens pouvaient contribuer à réduire l'accès involontaire ou inapproprié aux opioïdes et à agir en conséquence. Un éditorial précédent du J*ournal canadien de la pharmacie hospitalière* (JCPH) a souligné le besoin des hôpitaux canadiens et de leur service de pharmacie respectif de passer à la loupe les processus de manipulation des opioïdes et de remédier aux faiblesses qui pourraient faciliter le détournement de médicaments, il soulignait également le besoin de décrire les mécanismes potentiels pour y parvenir.[1] La SCPH a préparé un manuel de lignes directrices de 47 pages pour aider les services de pharmacie à protéger leur réseau de distribution de médicaments.[2] Le défi consiste maintenant à optimiser la thérapie opioïde pour le traitement de la douleur de chaque patient dans nos institutions et au-delà. Comment identifier les patients pris individuellement, les populations de patients ainsi que les environnements où l'usage des opioïdes est inapproprié, excessif ou propre au détournement?

Un tel examen des pratiques d'intendance des opioïdes au sein de chaque établissement peut sembler être une tâche colossale, mais les ressources permettant d'aider à identifier les patients commencent à être disponibles. Ailleurs dans ce numéro du JCPH, Woods et collab.[3] décrivent la mise au point d'un outil visant à identifier les patients qui présenteraient des risques d'effets indésirables découlant des opioïdes dans différentes unités de soins hospitaliers. Ils indiquent que les pharmaciens praticiens ont trouvé que l'outil – qui décrit les facteurs de risque d'issue indésirable résultant des opioïdes et les interventions correspondantes potentielles visant à les réduire – était utile mais potentiellement difficile à intégrer dans la pratique de tous les jours.[3] Avec un peu de chance, ces enquêteurs évalueront son impact sur l'utilisation des opioïdes au sein de leur établissement et feront part de leurs découvertes à l'occasion d'un article ultérieur. Il ne s'agit là que d'un exemple d'outils et d'autres ressources qui sont désormais disponibles pour établir ou renforcer un programme de gestion des opioïdes.

La maximisation de l'impact des initiatives d'intendance, nécessite la coordination des cliniciens clés, des administrateurs et du personnel responsable de l'évaluation de la qualité au sein de toutes les institutions ou de tout le système de soins. Deux articles récemment publiés rapportent des discussions approfondies et illustrées d'exemples sur la structure administrative, les disciplines et les tâches recommandées pour effectuer le changement désiré dela culture de l'utilisation des opioïdes dans un environnement de soins de santé.[4,5] Les pharmaciens ne devraient pas et ne peuvent pas affronter seuls les problèmes posés par l'intendance des opioïdes. En lieu et place, ils devraient utiliser leur expertise en matière de gestion de la douleur, d'optimisation de la pharmacothérapie et de formation des cliniciens et des patients pour instruire l'ensemble de la communauté des soins sur leur utilisation. Les auteurs de ces deux articles proposent que tout programme d'intendance devrait, le cas échéant, explorer et adopter des méthodes visant à utiliser des analgésiques non opioïdes en première ligne et à établir des processus (pour la sélection, les doses, les durées, les voies d'administration ou l'abandon de médicaments) pour une utilisation optimale de tout traitement opioïde jugé essentiel.[4,5]

Les stratégies visant à entreprendre des traitements non opioïdes contre la douleur exigent l'accord de toutes les disciplines impliquées dans les soins des patients souffrant de diverses pathologies douloureuses. Les pharmaciens peuvent participer à l'examen des indications et de l'efficacité des produits non opioïdes pour le traitement de pathologies particulières et potentiellement le mener. Grâce à leur évaluation de la documentation publiée et à leur compétence en matière d'enseignement, les pharmaciens sont des contributeurs clés à l'atteinte d'un consensus entre les cliniciens sur l'utilité et l'efficacité du traitement non opioïde.

Les pharmaciens peuvent aussi être des contributeurs clés pour déterminer les méthodes visant à réduire l'exposition des patients aux opioïdes durant leurs interactions avec les établissements de soins de santé. De tels processus pourraient impliquer l'utilisation du système de distribution des pharmacies pour identifier les patients qui reçoivent plus d'un opioïde administré par une même voie. Pour les patients hospitalisés, limiter l'importance des gammes de dosages, limiter à des scénarios particuliers la mise en place de l'administration parentérale et renforcer la vigilance lors de l'administration des préparations à action prolongée (timbres ou formules orales à libération prolongée) sont des exemples de processus que les pharmaciens pourraient utiliser pour réduire le risque associé à toute utilisation obligatoire d'opioïde.[6] Autrement, l'examen de la quantité d'opioïde fournie au moment du congé, mené par le pharmacien, pourrait permettre de déterminer les occasions de réduire l'exposition à cette substance, bien que la réussite de cette approche n'ait pas été démontrée dans tous les contextes.[7] Un groupe de pharmaciens de Minneapolis (Minnesota) a publié une description approfondie des attentes liées aux examens de tous les traitements opioïdes faits par les pharmaciens au sein de leur établissement.[6] Elle peut servir de point de départ fiable pour les pharmaciens canadiens souhaitant déterminer des attentes réalistes.

Les pharmaciens peuvent également influencer l'utilisation des opioïdes au moyen d'activités pédagogiques destinées aux fournisseurs de soins et aux patients. Des chercheurs de London (Ontario) ont démontré que l'instruction donnée aux cliniciens et aux patients, de concert avec des stratégies établies en matière d'analgésiques, pouvait réduire les besoins en matière d'opioïdes des patients ayant subi divers types d'interventions chirurgicales.[8,9] Les offres pédagogiques des pharmaciens pourraient couvrir des thèmes tels que l'évaluation de la douleur, les schémas thérapeutiques, l'entreposage et l'élimination sécuritaire des produits stupéfiants.[4] L'instruction donnée aux patients ambulatoires concernant l'utilisation appropriée de la naloxone et l'enseignement des méthodes visant à déceler et à résoudre les symptômes de sevrage aux opioïdes sont des domaines supplémentaires qui pourraient tirer profit de l'expertise des pharmaciens.[5]

Il existe un grand besoin d'interventions et la palette des interventions est vaste. Il est grand temps désormais que les services de pharmacie et les pharmaciens encouragent leurs communautés de soins (hôpitaux ou réseaux de soins de santé) à établir et à mettre en place des stratégies d'intendance efficaces en matière d'opioïdes. Une fois lancées, de telles initiatives ne réussissent que si des processus sont eux aussi définis pour pouvoir mesurer et évaluer en continu l'impact de ces efforts sur l'utilisation des opioïdes.[7] Des cliniciens de Houston au Texas ont récemment publié leurs recommandations accompagnées de commentaires d'autres cliniciens. Elles portaient sur 19 indicateurs de qualité qui pourraient être utiles pour mesurer les effets continus et soutenus des activités d'intendance des opioïdes.[10] Tous les pharmaciens institutionnels canadiens sont invités à dépasser la discussion sur les avantages potentiels de la mise en place d'actions pour optimiser l'utilisation des opioïdes par leurs patients. Simplement dit, il est temps de passer à l'action. En acquérant de l'expérience dans ce domaine, veillez à mesurer vos réussites et vos échecs et expliquez vos techniques aux autres pour que nous puissions tous apprendre « le comment » de la bonne intendance en matière d'opioïdes.

[Traduction par l'éditeur]

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Designing a Pharmacist Opioid Safety and Intervention Tool

Brendan Woods, Michael Legal, Stephen Shalansky, Tamara Mihic, and Winnie Ma

ABSTRACT

Background: Despite the recent increase in opioid overdoses across Canada, few pharmacy-led initiatives have been implemented to address issues related to opioid prescribing in the hospital setting.

Objectives: The primary objective of this study was to develop a clinical tool, intended for use by hospital pharmacists and informed by best practices from the literature, that would provide a structured approach to enhancing the safety of opioid prescribing. The secondary objective was to collect pharmacists' opinions about the feasibility and utility of this tool.

Methods: A comprehensive literature search and pharmacist focus group analysis provided content for development of a candidate clinical tool. This tool was then piloted by clinical pharmacists working on general medical and surgical units in a single hospital. Pharmacists participating in the pilot were invited to complete an online survey concerning their perceptions of the tool. Descriptive statistics were used to analyze the survey results.

Results: The literature search and focus group analysis led to development of a candidate clinical tool that focused on Medication review, Optimization, Reassessment, and Education (MORE). It included key risk factors relating to opioid safety, along with suggested mitigating strategies. The MORE tool was piloted for 3 weeks by 14 clinical pharmacists, 9 of whom responded to the subsequent survey. Five respondents indicated that the clinical tool increased their ability to identify risk factors. Five respondents also noted an increase in their ability to identify possible interventions. Most respondents felt that the tool was useful and that it would be feasible to integrate it into their practice; however, they noted that a more streamlined version could improve ease of use.

Conclusions: The MORE tool was well received by clinical pharmacists. Implementation of the tool into routine practice requires additional changes to improve ease of use. Suggestions for modifying and streamlining the tool will be incorporated into future versions.

Keywords: opioids, pharmacist, stewardship, clinical tool

RÉSUMÉ

Contexte : Malgré l'augmentation récente des surdoses d'opioïdes au Canada, peu d'initiatives menées sous la houlette de pharmacies ont été mises en place sur les enjeux potentiels liés à la prescription d'opiacés en milieu hospitalier.

Objectifs : L'objectif principal de cette étude visait à élaborer un outil destiné aux pharmaciens d'hôpitaux, s'inspirant des meilleures pratiques rapportées dans la documentation, qui fournirait une approche structurée pour améliorer la sécurité de la prescription d'opioïdes. L'objectif secondaire consistait à recueillir les opinions des pharmaciens sur la faisabilité et l'utilité d'un tel outil.

Méthode : Des recherches bibliographiques étendues ainsi qu'une analyse de groupes de discussion de pharmaciens ont fourni le contenu nécessaire à l'élaboration d'un outil clinique expérimental. Ensuite, cet outil a été testé par des pharmaciens cliniciens travaillant dans des unités médicales générales et chirurgicales au sein d'un seul hôpital. Les pharmaciens participant au projet pilote ont été invités à répondre à une enquête en ligne sur leur perception de l'outil. Des statistiques descriptives ont permis d'analyser les résultats de l'enquête.

Résultats : Les recherches bibliographiques et l'analyse des groupes de discussion ont débouché sur le développement d'un outil clinique nommé MORE [pour *Medication review, Optimization, Reassessment, and Education*, ou Examen, optimisation, réévaluation et éducation aux médicaments]. Il comprenait des facteurs de risque liés à la sécurité des opioïdes ainsi que des suggestions de stratégies d'atténuation. Quatorze pharmaciens cliniciens, dont neuf ont répondu à l'enquête qui a suivi, ont testé le MORE pendant trois semaines. Cinq répondants ont indiqué que l'outil clinique augmentait leur capacité à déterminer les facteurs de risque. Cinq ont également noté une meilleure capacité à déterminer les interventions possibles. La plupart des répondants ont estimé que l'outil était utile et qu'il serait possible de l'intégrer dans leur pratique; cependant, ils ont aussi noté qu'une version simplifiée pourrait faciliter son utilisation.

Conclusions : Les pharmaciens cliniciens ont bien accueilli l'outil MORE. Sa mise en œuvre dans la pratique courante exige cependant des changements supplémentaires pour faciliter son utilisation. Les versions à venir tiendront compte des propositions visant à le modifier et à le simplifier.

Mots-clés : opioïdes, pharmacien, intendance, outil clinique

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INTRODUCTION

The opioid crisis has had an immense impact on the individuals affected, their families, and the health care system, including in the province of British Columbia.[1] A recent report published by the government of Canada stated that there were 13 900 opioid-related deaths in Canada between January 2016 and June 2019.[2] An average of 4 deaths each day in British Columbia are due to opioid overdoses, and the proportion of emergency department visits attributed to opioid overdose is as high as 25% in some centres.[3,4] Contamination of the illicit drug supply with fentanyl has been a major driver of overdose deaths.

Previous studies have suggested that individuals who misuse prescription opioids are more likely to turn to illicit street drugs that put them at risk for overdose.[5] Canada is currently second only to the United States in the number of opioid prescriptions written per capita, and in the past 12 years the quantity of opioids prescribed has tripled across the country.[6,7] Prescribing of opioids upon hospital discharge has been associated with a 5-fold higher rate of chronic opioid use and a greater risk of adverse effects and overdose among previously opioid-naive patients, compared with those who did not receive opioids upon discharge from hospital.[8] This suggests that intervening on inappropriate opioid prescriptions may help to decrease chronic opioid use and progression to opioid use disorder. A document produced by the University of Massachusetts provides support for a prevention-focused model regarding opioid misuse.[9]

A variety of community programs have been implemented to help address the opioid crisis, but few initiatives have targeted hospital practice. The Canadian Society of Hospital Pharmacists recently released a guideline addressing proper inventory management, dispensing, and distribution of opioid medications in hospitals and other health care settings.[10] However, when we initiated the present study, no formal pharmacist-led clinical programs focusing on in-hospital opioid prescribing had been implemented in Canada.

In the United States, some efforts have been made to promote optimal opioid use in the hospital setting. A pharmacist-led pain management stewardship program in Minnesota involved medication reconciliation, care plan guidance, and decentralized rounding for patients with prescriptions for long-acting oral opioids, high-dose opioids, methadone, and fentanyl.[4] Over a 1-year period, 16% of all patients admitted to the hospital were reviewed, and pharmacists made interventions for 44% of these patients.[4] A similar approach customized for the patient population in the authors' institution could be beneficial.

St Paul's Hospital is a 430-bed inner city tertiary care teaching hospital in Vancouver, British Columbia. The opioid crisis has had a major impact in the local community, and the hospital's clientele includes a significant proportion of patients with active opioid use disorder. Unpublished data from St Paul's Hospital indicated that 50% of patients receive a prescription for an opioid during their hospital admission. To date, no new resources have been provided to target opioid prescribing in the hospital or at discharge. Therefore, there is a need to empower existing staff to optimize opioid prescribing, especially for patients who have risk factors for opioid-related adverse events. This study aimed to develop a literature-informed clinical tool centred around best practices, to assist hospital pharmacists in identifying risk factors in their patients and to provide guidance on possible interventions to address these risk factors. Such an approach could provide a framework for other groups across the country to emulate. The secondary objective of the study was to pilot the tool and assess its usability and the feasibility of incorporating it into daily practice.

METHODS

Scope

The research team elected to target the proposed clinical tool toward pharmacists caring for patients on general inpatient medical and surgical wards. Patients in critical care areas and the emergency department and those being treated by the palliative care team have specific needs related to opioid analgesia; therefore, pharmacists working in these areas of the hospital were excluded from the pilot phase of the study. Participating pharmacists were also instructed to avoid applying the tool for patients being followed by the addiction medicine, acute pain, and chronic pain services, so as to focus efforts on patients who did not already have experts assessing their opioid therapy. Finally, because St Paul's Hospital does not have a dedicated oncology unit or service, patients with cancer-related pain are sometimes encountered but represent only a minority of admissions. No specific guidance was built into the tool to differentiate between patients with non-cancer pain and those with cancer-related pain.

Design

Development of the final tool involved 4 separate phases (Figure 1). Phase 1 was intended to inform the tool content and context through literature searches and focus groups of clinical pharmacists. Phase 2 focused on formulation of the clinical tool itself. Phase 3 involved piloting the candidate clinical tool, and Phase 4 involved deployment of a survey to participating pharmacists to gauge their perceptions of it (especially pertaining to usability and feasibility). The study protocol was approved by the local Behavioural Research Ethics Board, and informed consent was obtained from all pharmacist participants before their involvement in the study.

Phase 1: Informing Tool Content and Context

A literature search was conducted to answer 3 key questions:

1. Which patient-specific factors or characteristics are associated with an increased risk of adverse outcomes in patients for

whom opioids are prescribed (e.g., opioid overdoses, hospital admissions, substance use disorders)?
2. Which opioid prescribing practices/patterns are associated with an increased risk of adverse outcomes?
3. Which interventions (pharmacy-based or otherwise) have been shown to mitigate the risks described in questions 1 and 2?

Two members of the research team (B.W., M.L.) searched multiple databases, specifically Ovid MEDLINE, PubMeb, Embase, CINAHL, and Google Scholar, with date limits from 1960 to 2017. All article types were included. The search was comprehensive but was not intended to be a formal systematic review of the literature. The search terms were "opioid" or "opioid analgesics", "prescribing" or "inappropriate prescribing", "risk factors" or "risk assessment", "prescription drug misuse" or "misuse", "hospital", "pharmacist", "interventions", "opioid stewardship", and "adverse drug events". The investigators manually screened the search results and further refined the search in an iterative manner. Relevant studies were summarized to produce a list of risk factors for opioid misuse/use disorder and other adverse events, inappropriate prescribing practices, and interventions utilized at other sites to promote opioid stewardship and safety.

In addition to the literature search, 3 focus groups involving clinical pharmacists were conducted at St Paul's Hospital. The pharmacist focus groups were intended to gauge pharmacists' baseline perspectives about the need for an opioid stewardship program or intervention, the role that pharmacists should have in such a program, potential barriers to implementation, and key content to consider in tool development. Each focus group was scheduled for 30 minutes and involved at least 4 clinical pharmacists across a variety of specialties. Pharmacists were invited via an e-mail message distributed to all clinical pharmacists (using a "blind cc" distribution list) by pharmacy administration. A structured question list (Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc) was used, and at least 1 facilitator and 1 transcriber from the research team were present at each session. Each session was audio-recorded (with the verbal and written consent of all participants), and the transcriber who was present during the session reviewed the recording and transcribed it verbatim. The transcripts were then analyzed using the Theoretical Domains Framework, a validated tool for the qualitative analysis of focus groups.[11,12] Each transcript was analyzed independently by at least 2 members of the research team, and each participant utterance was coded using the Theoretical Domains Framework. In the case of discrepancies in coding, the 2 team members first attempted to resolve them through discussion; if a consensus was not reached, a third member of the team made the final decision.

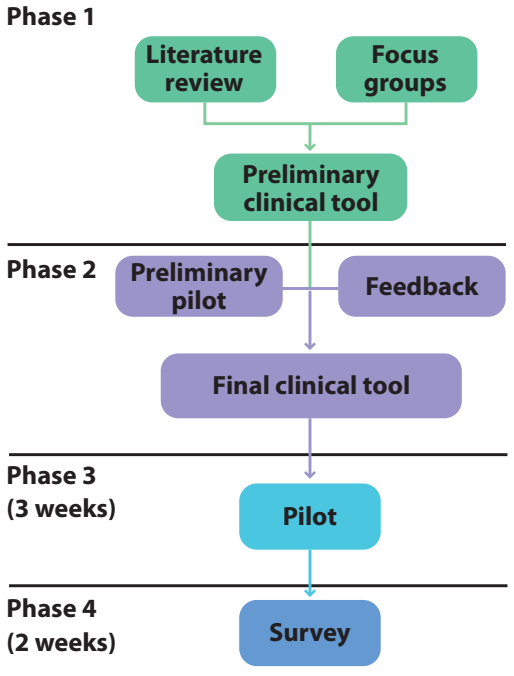

Figure 1. Phases of the study.

Phase 2: Formulating a Preliminary Clinical Tool

Using the content gathered in phase 1, the research team developed a preliminary clinical tool. Principles considered in designing the tool included provision of a simple stepwise approach in the form of a 1-page reference that pharmacists could bring with them to the patient care unit. It was also important that the tool be suitable for assisting pharmacists to quickly identify patient risk factors and suboptimal opioid prescribing and then offer strategies to optimize therapy and mitigate risk. Finally, the tool was intended to blend literature-derived risk factors and interventions with practical approaches and considerations supplied by the clinical pharmacist focus groups. A draft of the preliminary tool was provided to a physician specializing in addictions for review and feedback. The preliminary tool was also field-tested by 4 clinical pharmacists who used the tool for 1 day each in their practice. Once final edits were made to the tool, the final "candidate tool" was ready for the larger pilot in phase 3.

Phase 3: Piloting the Clinical Tool

The candidate clinical tool was shared with clinical pharmacists working on general medical and surgical wards in the study hospital, who piloted it as a part of their routine clinical care for a defined 3-week period in February 2018. As described above, clinical pharmacists working in critical care, the emergency department, and palliative care units of the hospital were excluded from the pilot, and the tool was not applied to any patients who were being followed by the addictions or pain consult services. Pharmacists were asked to use the tool to guide patient assessment

when any one of the following conditions was met: a combination of opioid and benzodiazepine was ordered, a regularly scheduled opioid medication was ordered, or opioids were ordered for use on an as-needed basis for more than 5 days. These criteria were chosen to maximize pharmacist impact, given that the pilot activities were additional to their existing clinical responsibilities.

Phase 4: Capturing Feedback on the Clinical Tool via Survey

An online survey was developed by the research team and administered using the Qualtrics Survey tool (first release 2005; Qualtrics, Provo, Utah; https://www.qualtrics.com). The survey included multiple-choice questions relating to the logistics of tool deployment, such as area of care, patient count, and criteria for application of the tool (as described in the previous subsection). It also included Likert-scale questions aimed at assessing pharmacists' perceptions of the tool in terms of facilitating identification of risk factors and interventions, tool usability, and feasibility of incorporating the tool into practice. The questions relating to pharmacists' perceptions of the tool and associated responses are presented in Appendix 2 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc). Respondents were also asked to provide free-text suggestions about how the tool could be improved.

All participants in the pilot trial were invited to participate in the survey; a link to the online survey was sent via e-mail within a 14-day window after completion of the pilot period. No identifying information was gathered in the survey. The survey remained open for a 14-day period, and participants were reminded to complete the survey via an email message sent at the 7-day mark.

RESULTS

Phase 1: Informing Tool Content and Context

Literature Search

The literature search and screening yielded 14 editorials and guidelines, 79 articles pertaining to risk factors or inappropriate prescribing practices, and 3 articles (all from the United States) describing opioid stewardship initiatives. There was significant duplication and overlap in terms of the risk factors identified in the studies; a selection of the most commonly identified risk factors (both non-modifiable and modifiable) and representative studies are summarized in Appendix 3 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc). Examples of non-modifiable risk factors were history of substance use disorder, psychiatric diagnoses, age, absence of prior exposure to opioids, and impaired renal or hepatic function. Modifiable risk factors included excessive opioid dose or frequency, use of parenteral route, prescribing of multiple types of opioids, and use of long-acting opioids for acute pain. Suboptimal combinations of opioids with benzodiazepines and long-acting/short-acting opioid combinations were also identified as risk factors for opioid-related adverse events.[13,14] Ultimately, the risk factors chosen for inclusion in the final tool were those frequently cited in the literature and feasible for clinical pharmacists to capture in an inpatient setting. The literature search did not identify any formalized Canadian pharmacy-led approaches to opioid stewardship. Formal programs have been initiated in the United States, but long-term data on patient outcomes have yet to be published.

Focus Groups

Thirteen clinical pharmacists with work experience ranging from 1 to 30 years participated in a total of 3 focus groups. The key themes arising through analysis with the Theoretical Domains Framework[11] are presented in Appendix 4 (available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc). Several themes were identified, such as ensuring that pain management is not compromised during opioid stewardship. Focus group participants also expressed a desire to ensure that the program or tool would not overly emphasize avoiding or limiting opioids. Instead, participants felt that it should promote appropriate use of opioids and non-opioid alternatives, with the goal of optimizing pain management. Participants also recognized the significant clinical and environmental context at play when addressing the use of opioid medications. Participants felt that they were sometimes limited by a lack of time and resources to optimize pain control for every patient. Concerns were also raised about barriers pertaining to hospital policy and interprofessional collaboration, with recognition that a pharmacist's clinical area, workload, and local team dynamics could also play a role. It was also recognized that it may be challenging to ensure that medication changes made in hospital are appropriately communicated to community providers. The pharmacists provided a number of practical suggestions about risk factors for inclusion in the tool and strategies to optimize medication use. Additionally, the participants indicated that it might be useful to supplement the tool with educational resources for both patients and interprofessional collaborators.

Phase 2: Formulating the Clinical Tool

Using the principles outlined in the Methods section and incorporating the results from phase 1, the research team formulated a preliminary clinical tool. The addictions physician reviewed this preliminary tool, endorsed the content, and suggested minor revisions. The tool was then refined through a series of single-day test cycles involving 4 medical and surgical pharmacists. On the basis of this testing, the tool's formatting was improved, and some of the wording was simplified. The final candidate MORE tool is shown in Appendix 5 (available at https://www.cjhp-

online.ca/index.php/cjhp/issue/view/195/showToc). The MORE tool focuses on a 4-point process for evaluation of opioid medications: medication and safety review (M); optimization of pain medications (O); reassessment and risk referral (R); and education, planning, and communication (E).

Phases 3 and 4: Piloting the Clinical Tool and Capturing Feedback via Survey

A total of 14 pharmacists piloted the candidate MORE tool over the course of 3 weeks; the survey was deployed after this pilot period. Nine pharmacists responded to the survey, and these pharmacists had used the tool to assess a total of 33 patients. The 9 respondents indicated that they had reviewed at least 1 to 3 of their patients per week. Five of the 9 respondents thought that the criteria for selecting patients were too limiting, 2 respondents thought the criteria were appropriate, and 2 respondents thought they were too broad.

The survey also asked for respondents' opinions about having the pharmacy computer system generate an automated report to assist them in identifying patients for review. Five of the 9 respondents felt that such a report would be useful, and 6 indicated they would prefer that the program generating the report be run at least once per week.

The questions about pharmacists' perceptions of the tool and the distribution of responses are outlined in Appendix 2. Five of the 9 respondents indicated that the MORE tool had a positive impact on their ability to identify risk factors. The most frequently identified risk factors were lack of adjunct pain medications and non-modifiable risk factors such as advanced age, renal or liver dysfunction, and prior history of opioid use disorder. Five of the 9 respondents described the MORE tool as helpful in identifying possible interventions. The interventions that pharmacists considered most feasible were making recommendations for adjunctive non-opioid pain medications and making recommendations for medications to treat adverse effects of opioids, such as constipation or pruritus.

Eight pharmacists provided responses relating to ease of use of the tool. Four of these respondents felt that the tool was "slightly difficult to use", whereas the other 4 indicated their perception that the tool was easy to use. All 8 respondents indicated that it would be feasible to integrate the tool into their clinical practice. Five of the 8 respondents described the tool as moderately useful (n = 4) or very useful (n = 1) in improving the management of care for patients receiving opioids, whereas 3 described it as slightly useful.

Participants also provided qualitative responses regarding the feasibility and usability of the tool. Several described the tool as being "too busy" or "too wordy", and one indicated that a "slimmer version would be nice". Another stated that "The biggest challenge is balancing this new initiative with existing work that we need to do." Multiple respondents indicated that the risk factor and intervention checklists were the most useful parts of the tool. One respondent indicated that information regarding "when to refer to different services" was useful. When asked what could be improved, respondents indicated that "the tool could be broken down into more clear steps" and also suggested "having a secondary form to document ongoing monitoring". When prompted for suggestions on additional materials that would help pharmacists to support opioid stewardship, respondents indicated that "counselling sheets for patients on discharge might be helpful", "a laminated card with quick facts" might be beneficial, and "more education and awareness" would be valuable.

DISCUSSION

Current literature states that the misuse of opioid medications in Canada is leading to significant morbidity and mortality. Collectively, health care professionals (including pharmacists) have acknowledged that misuse of opioids is one of the leading health issues in the country.[10] To our knowledge, this is the first opioid safety and intervention tool developed for use by hospital pharmacists. Best practices were integrated into the tool to help pharmacists efficiently identify risk factors in their patients and to highlight interventions to avoid opioid-related adverse events. The tool also provides guidance on patient counselling and on ensuring community follow-up for high-risk patients.

Overall, the pharmacists who were involved in the pilot and who responded to the survey felt that the tool helped them to identify risk factors in their patients. They also commented that having a quick reference table helped in the selection of appropriate interventions to optimize therapy and address risk factors. The pharmacists identified several barriers to using the tool, such as time constraints and competing workload in their daily practice. This feedback highlights the potential need for dedicated opioid stewardship resources. Several participants had concerns about the usability of the tool. These concerns seemed to be primarily related to the large amount of information included in the tool. Although it is possible that with repeated use the pharmacists might have become more accustomed to using the tool, the feedback clearly indicates a need to streamline the tool. A logical approach would be to preserve the risk factor assessment and order optimization components of the tool while reducing extraneous information that could be easily located through other reference sources. For example, the detailed information about managing opioid-related adverse effects could be removed from the tool.

We believe that in the context of the current opioid crisis, a streamlined version of the MORE tool could be very useful to hospital pharmacists locally and across Canada. Although the tool was developed at a single centre and was piloted by pharmacists working primarily on general medical and surgical units, the risk factors and interventions included in the tool are broadly applicable. Pharmacists form an integral part of patient-centred health

care teams and are well positioned to optimize pain management while ensuring the safe use of opioids when such medications are necessary. As such, the MORE tool could provide a catalyst to promote pharmacists as leaders in opioid stewardship.

This study had a number of potential limitations. Although development of the tool was informed by the literature and input from clinical pharmacists, there was some subjectivity in prioritizing the risk factors and interventions and in the overall design of the tool. This study assessed clinical pharmacists' perceptions of the MORE tool but was not designed to assess clinical outcomes such as quality of pain management or frequency of opioid-related adverse events. Five of the 14 pharmacists who piloted the tool did not complete the survey. The reasons are unclear, but may be related to competing responsibilities or their work schedules. Finally, the tool is not intended for patients with cancer-related or end-of-life pain or for patients in critical care or the emergency department and was not evaluated in these settings.

CONCLUSION

Our research team developed an opioid safety and intervention tool that was well received in a pilot study of clinical pharmacists. The tool was particularly helpful in identifying risk factors and possible interventions for patients with non-malignant pain admitted to general medical and surgical units. The results indicate that streamlining the information and design would improve the overall usability of the tool and its acceptance by clinical pharmacists.

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Real-World Budget Impact of Listing a Biosimilar of Rituximab

Arnaud Boidart, Martin Darveau, Nicole Déry, and Marie-Claude Racine

ABSTRACT

Background: The approval of new biosimilars by national health agencies is expected to generate significant cost savings for health care systems. This is particularly the case with the biosimilar of rituximab approved for the Canadian market in 2019. However, several uncertainties remain regarding utilization of this agent.

Objectives: To determine the proportion of total annual drug expenses for each indication for rituximab in the hospital setting and to determine potential savings related to introduction of a biosimilar.

Methods: A budget impact analysis was performed through 3 real-world scenarios, based on data obtained from a large university teaching hospital for a 12-month period.

Results: This study involved data for 420 patients. Annual expenses for rituximab for all indications represented 7.7% of total annual drug spending for the hospital, of which 5.0% was related specifically to indications approved by Health Canada. More than 6% of the annual drug expenses was attributable to the use of rituximab for oncologic indications, including 1.8% for uses not approved by Health Canada. Overall, each 10% reduction in the price of a biosimilar of rituximab (relative to the reference rituximab) would result in annual savings of about 0.8% of total drug expenses in the hospital if a biosimilar was used for all real-world indications, whether approved by Health Canada or not.

Conclusions: The introduction of a biosimilar of rituximab to the Canadian market would generate significant savings. To properly assess the potential savings that this agent could generate in the limited budget environment of a hospital, it seems important to consider all of the indications for which it could be used.

Keywords: biosimilar, rituximab, budget impact analysis, hospital setting, real-world analysis

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RÉSUMÉ

Contexte : On s'attend à ce que l'approbation de médicaments biosimilaires par les agences de santé nationales génèrent des économies importantes pour les systèmes de soins de santé. C'est particulièrement le cas pour le biosimilaire du rituximab approuvé pour le marché canadien en 2019. Cependant, plusieurs incertitudes demeurent quant à son utilisation.

Objectifs : Déterminer la proportion des dépenses pour chaque indication du rituximab par rapport à la dépense totale annuelle en médicaments dans un contexte hospitalier et déterminer les économies potentielles liées à l'introduction d'un biosimilaire.

Méthode : Une analyse d'impact budgétaire a été réalisée à partir de trois scénarios basés sur des données obtenues dans un grand centre hospitalier universitaire sur une période de 12 mois.

Résultats : Cette étude a examiné les données de 420 patients. Les dépenses annuelles relatives au rituximab, toutes indications confondues, représentaient 7,7 % des dépenses annuelles totales de l'hôpital. De celles-ci, 5 % étaient liées en particulier aux indications approuvées par Santé Canada. Plus de 6 % des dépenses annuelles en médicaments étaient imputables à l'utilisation du rituximab à des fins oncologiques, y compris 1,8 % pour des utilisations que Santé Canada n'a pas approuvées. De manière générale, chaque réduction de 10 % du prix d'un produit biosimilaire du rituximab (parent du rituximab référence) entraînerait des économies annuelles d'environ 0,8 % du total des dépenses en médicaments dans cet hôpital si les produits biosimilaires étaient utilisés pour toutes les indications, qu'elles soient approuvées ou non par Santé Canada.

Conclusions : L'introduction d'un biosimilaire du rituximab sur le marché canadien engendrerait des économies importantes. L'évaluation adéquate des économies générées par un biosimilaire pour un hôpital ayant un budget limité nécessite la prise en compte de toutes les indications pour lesquelles il pourrait être utilisé.

Mots-clés : biosimilaire, rituximab, analyse d'impact budgétaire, environnement hospitalier, données en situation réelle

INTRODUCTION

Controlling drug expenses is an important issue for hospitals. Continual efforts are made by clinical teams to offer the best treatment at the lowest cost. Indeed, hospital pharmacies are constantly working to put in place mechanisms to optimally manage drug costs. In recent years, actions undertaken at both clinical and administrative levels may have prevented annual drug expenses from exceeding the allocated annual drug budget in some hospitals. Nowadays, hospitals are confronted with legislative and administrative considerations that have changed the environment in which pharmacy departments are operating in the province of Quebec. As a result, drug-related spending will become increasingly difficult for hospitals to control.

The arrival of some biosimilars on the Canadian market in the coming years may allow some control of drug expenses in the hospital setting. However, several uncertainties remain regarding utilization of these agents. A biosimilar is evaluated by legal authorities using thorough and rigorous analyses to confirm its structure, function, clinical efficacy, and safety are similar to those of its originator biological.[1,2] However, there are many practical considerations, such as interchangeability, substitution, indication extrapolation, and logistics of product use and reimbursement, that may affect willingness to use a biosimilar for a particular indication.[3] More importantly, the use of a biosimilar is linked to its indications approved by Health Canada. However, scientific evidence might justify use of the reference product for some indications for which Health Canada has not granted approval, and the propensity of clinicians to prescribe a biosimilar for these non-approved indications is an important issue in the hospital setting.[4,5]

When a drug enters the Canadian market, the Patented Medicine Prices Review Board (PMPRB) generates a budget impact analysis. In most cases, this analysis estimates the economic effect of using the drug for Health Canada–approved indications. Hence, for some medications, this analysis cannot be applied "as is" to assess the impact on a hospital's budget, because the drug may be used for other conditions that have not been approved by Health Canada. This is particularly the case for the licensed biologic rituximab (Rituxan®, Hoffmann-La Roche Ltd, Mississauga, Ontario).[6-9]

Rituximab is a chimeric monoclonal antibody that specifically binds to the CD20 transmembrane antigen on mature pre-B and B lymphocytes. It is approved by Health Canada for the treatment of non-Hodgkin lymphoma, rheumatoid arthritis, chronic lymphocytic leukemia, granulomatosis with polyangiitis (Wegener granulomatosis), and microscopic polyangiitis.[10] However, data may also support its use for other conditions,[11] such as immune thrombocytopenic purpura,[12-14] autoimmune hemolytic anemia,[15] glomerulonephritis,[16] and (particularly) some oncological conditions, including Waldenstrom macroglobulinemia[17] and malignancies other than low-grade or follicular non-Hodgkin lymphoma.[18,19] Indeed, rituximab has been identified as one of the most cost-generating drugs in our hospital, a large university teaching hospital in the province of Quebec, representing about 15% of annual expenses for drugs used in oncology and about 7.7% of total annual expenses for drugs.

The Biosimilars Initiative[20] was recently launched in the province of British Columbia. Under this initiative, the plan was to switch patients using etanercept, infliximab, or insulin glargine to biosimilar versions by November 25, 2019. As a result, British Columbia PharmaCare will cover costs only for the biosimilar versions. Other jurisdictions may decide to apply a similar policy, possibly extending it to all biosimilars, including those used in hospitals. Moreover, government authorities may even decide to completely delist the reference product. This could have an important effect on the management of these drugs in the hospital setting and could be of concern, particularly in oncology.

The current study was undertaken to explore how the arrival of a biosimilar of rituximab on the Canadian market could result in savings in the hospital setting, based on the indications for which it is likely to be used in the real world. This article should provide useful insights to anticipate future budget impacts, whether all uses would be linked to a preferred reimbursement policy or whether the decision to prescribe the reference product for some indications would be at the clinician's discretion.

METHODS

This study was conducted at the Centre hospitalier universitaire (CHU) de Québec–Université Laval, a large university hospital centre with 1263 beds. It is the largest hospital in the province of Quebec and one of the largest hospitals in Canada, serving a population of nearly 2 million. It offers a complete range of general, specialized, and ultra-specialized care and services. All adult patients (age ≥ 18 years) who received rituximab at the CHU de Québec–Université Laval were identified during 12 consecutive months (January 1 to December 31, 2016). For that period, the average dose (mg) per patient, the average number of doses per patient, the total number of doses, and the average total amount administered (mg) per patient were calculated. The therapeutic indications were determined and divided into 2 categories: indications approved by Health Canada and other uses. These indications were then grouped according to the following medical specialties: hematology, immunology, infectious diseases, nephrology, neurology, oncology, and rheumatology. The total drug cost of rituximab was calculated for each patient over the 12-month period and reported by indication. Because rituximab expenses remained stable from 2016 to 2019 and no new indication was authorized in the study hospital during this period, budget impact analyses were carried out using 2019 drug expense data (for April 1, 2018, to March 31, 2019). The proportion of annual expenses of rituximab for each therapeutic use was calculated in relation to total annual drug expenses.

Unlike pharmacoeconomic studies, budget impact analysis considers only drug cost. Therefore, no safety or efficacy data were taken into account in this analysis. Moreover, because both products have the same concentration and volume, there was no cost accounting for waste due to incomplete use of vials. In other words, under this analysis, one vial of the biosimilar was assumed to replace one vial of the reference product.

Regarding market share, various scenarios were considered. The first scenario reflects the situation in which the biosimilar of rituximab would benefit from a preferred reimbursement policy and would capture the whole market of the reference rituximab for 100% of the indications recognized by Health Canada in the hospital setting. The second scenario evaluates the additional budget impact of using a biosimilar of rituximab for each non-approved indication, grouped by medical specialties. Finally, the third scenario describes the situation in which the biosimilar of rituximab would replace the reference rituximab for all indications and uses, whether approved by Health Canada or not.

Summary statistics are presented for all variables. Numbers of patients and means with standard deviations (SDs) are displayed for continuous variables when the assumptions of normal distribution of data were met. Frequencies and percentages are provided for categorical variables.

RESULTS

A total of 436 patients were identified as having had a prescription for rituximab between January 1 and December 31, 2016. Six of these patients were excluded from the analysis because their data were incomplete, and 10 patients who were less than 18 years of age were also excluded. As a result, data for 420 patients were included in the analysis. The mean age of patients was 63.6 (SD 13.7) years, and 237 (56%) of the patients were men.

Table 1 shows the therapeutic uses for which the reference rituximab was administered in the study hospital and the proportion of spending for each indication. The indications approved by Health Canada accounted for 59.8% of cases. Only 1 patient (0.2%) received rituximab for treatment of rheumatoid arthritis, which might seem to indicate that the field of rheumatology was underrepresented in the analysis. However, this did not affect the external validity, because rituximab is usually administered outside the hospital setting for this indication. Other (non-approved) uses represented 40.2% of the cases.

Overall, oncologic indications represented the vast majority of the cases (80.7%), including 58.6% for indications approved by Health Canada and 22.1% for indications without Health Canada approval but supported by the literature. Several other

Table 1. Therapeutic Uses of and Spending on Rituxan® in the Study Hospital

Therapeutic Use	No. (%) of Patients	Dose per Patient (mg) (Mean ± SD)	No. of Doses per Patient (Mean ± SD)	Annual Expenses	
				% of Total Rituxan® Spending	% of Total Drug Spending
Indications approved by Health Canada					
Total approved indications	251 (59.8)	701.8 ± 106.6	4.5 ± 2.2	64.3	5.0
Wegener granulomatosis	4 (1.0)	925.0 ± 129.9	3.5 ± 0.5	1.0	0.1
Oncology	246 (58.6)	697.0 ± 100.6	4.5 ± 2.2	63.1	4.9
CLL	33 (7.9)	793.4 ± 150.7	4.8 ± 2.1	10.6	0.8
NHL, low grade	14 (3.3)	659.4 ± 79.8	4.8 ± 2.4	3.5	0.3
NHL, diffuse large B-cell	111 (26.4)	680.6 ± 81.8	4.4 ± 2.2	26.9	2.1
NHL, follicular	88 (21.0)	687.4 ± 78.5	4.5 ± 2.2	22.1	1.7
Rheumatoid arthritis	1 (0.2)	1000.0 ± 0.0	2.0 ± 0.0	0.2	NS
Non-approved uses (by medical specialty)					
Total non-approved uses	169 (40.2)	739.3 ± 149.4	3.7 ± 2.3	35.7	2.8
Hematology	27 (6.4)	681.5 ± 77.0	3.8 ± 1.1	5.6	0.4
Autoimmune hemolytic anemia	5 (1.2)	689.0 ± 104.1	3.4 ± 1.2	0.9	< 0.1
Immune thrombocytopenic purpura	17 (4.0)	684.4 ± 74.8	3.8 ± 1.1	3.6	0.28
Immunology	7 (1.7)	846.4 ± 186.0	2.4 ± 1.2	1.1	0.1
Infectious diseases	4 (1.0)	695.5 ± 117.2	3.8 ± 1.6	0.9	0.1
Nephrology (glomerulonephritis)	29 (6.9)	965.5 ± 126.7	1.8 ± 0.7	4.0	0.3
Neurology	8 (1.9)	789.5 ± 173.4	2.9 ± 2.1	1.4	0.1
Oncology	93 (22.1)	676.0 ± 76.7	4.4 ± 2.6	22.6	1.8
NHL malignancies other than low-grade or follicular	88 (21.0)	677.1 ± 76.3	4.4 ± 2.6	21.5	1.7
Rheumatology	1 (0.2)	652.0 ± 0.0	4.0 ± 0.0	0.2	NS
Total	420 (100)	716.9 ± 126.9	4.2 ± 2.3	100	7.7

CLL = chronic lymphocytic lymphoma, NHL = non-Hodgkin lymphoma, NS = not significant.

uses were identified. Among these, glomerulonephritis (6.9%) and idiopathic thrombocytopenic purpura (4.0%) were the most frequent. Most of the remaining indications represented less than 1% of cases each.

Annual expenses of rituximab for all indications represented 7.7% of total annual drug spending. Rituximab-related spending for indications approved by Health Canada represented 5% of total annual drug expenses. About 6.7% of annual expenses was attributable to the use of rituximab for oncologic indications, including 1.8% for uses not approved by Health Canada. Approximately 35% of annual expenses of rituximab were for other off-label uses, including 22.6% in oncology, 5.6% in hematology, and 4% in nephrology.

Table 2 shows the percentage savings from total annual drug expenses for each 10% reduction in the price of a biosimilar of rituximab relative to the price of the reference rituximab. Scenario 1 presents the situation in which a biosimilar of rituximab is used in the hospital setting only for indications approved by Health Canada. In this situation, each 10% decrease would generate annual savings of approximately 0.5% on total annual drug expenses. According to this scenario, the expected annual savings for a hospital having an annual drug expense of $50 million would be $248,809 per year (Table 3).

Scenario 2 shows the additional savings that would be generated with use of a biosimilar of rituximab not only for indications approved by Health Canada but also for other indications, based on real-world data observed in our university teaching hospital. For example, use of a biosimilar of rituximab for non-approved oncology indications would generate additional savings of 0.175% of total annual expenses for each 10% difference in price compared with the reference rituximab (Table 2 and Table 3).

Within the third scenario, overall, each 10% reduction in the price of a biosimilar of rituximab relative to Rituxan® would result in annual savings of about 0.78% of total annual drug expenses for this large university teaching hospital in the province of Quebec, if the biosimilar was used for all real-world indications, whether approved by Health Canada or not (Table 2).

Table 2. Impact of a Biosimilar of Rituximab on Total Annual Drug Expenses for a University Teaching Hospital in the Province of Quebec

Scenario	% Saving*
Scenario 1: Biosimilar of rituximab capturing market of reference rituximab for all indications approved by Health Canada	0.50
Scenario 2: Scenario 1 + savings due to biosimilar of rituximab replacing reference rituximab for each non-approved use (by medical specialty)	0.50 +
Oncology	0.175
Hematology	0.043
Nephrology	0.031
Immunology	0.008
Neurology	0.012
Infectious diseases	0.007
Rheumatology	0.002
Scenario 3: Biosimilar of rituximab replacing reference rituximab for all indications and uses, whether approved by Health Canada or not	0.78

*Savings in total annual drug expenses for each 10% reduction in the price of a biosimilar of rituximab, relative to the price of the reference drug, Rituxan®.

Table 3. Annual Savings with a 10% Reduction in Price of a Biosimilar of Rituximab Compared with Price of Rituxan®*

Scenario	Annual Saving
Scenario 1: Biosimilar of rituximab capturing market of reference rituximab for all indications approved by Health Canada	$248,809
Scenario 2: Scenario 1 + biosimilar of rituximab replacing reference rituximab for non-approved uses (by medical specialty)	$248,809 +
Oncology	$87,317
Hematology	$21,640
Nephrology	$15,376
Immunology	$4,129
Neurology	$5,317
Infectious diseases	$3,351
Rheumatology	$818
Scenario 3: Biosimilar of rituximab replacing reference rituximab for all indications and uses, whether approved by Health Canada or not	$386,759

*Based on hypothetical total annual drug expenses of $50 million.

DISCUSSION

Drug expenses represent a significant part of a hospital's budget. Despite the arrival of increasingly expensive drugs on the Canadian market, hospital pharmacies have, up to now, been able to control drug expenses. The arrival of generic oncology drugs and various clinical and administrative interventions have helped to offset the increase in prices. As a result, a slight decrease in total drug expenses was observed in our hospital from 2015 to 2017. However, among drugs representing a significant proportion of overall annual expenses, no generic drugs are anticipated on the Canadian market in the next few years.[21] Hence, the growing presence of more expensive drugs is no longer counterbalanced, and our hospital has experienced increases in drug expenses over the past few years. Conversely, the arrival of biosimilars could help to restore the economic counterweight that was previously exerted by generic drugs in the hospital setting.

As mentioned previously, much uncertainty remains about the introduction of biosimilars on the Canadian market in terms of their utilization, but also with regard to their price and the number of molecules becoming available. As reported in 2018 by the French Healthcare Products Pricing Committee (CEPS), the price of biosimilars in France was about 20% to 40% lower than that of the reference biologics.[22] In the province of Quebec, the biosimilar of bevacizumab, Mvasi™ (Amgen Canada Inc),[23] was

recently listed, with estimated provincial savings of $34.5 million over 3 years.[24] Furthermore, over the next 3 years in Canada, the PMPRB anticipates the arrival of about 10 biosimilar products.[25]

Regarding the rituximab situation specifically, the amount of savings that could be generated upon arrival of the biosimilar depends on 2 factors: price and utilization. Truxima™ (manufactured by Celltrion Healthcare Co Ltd and distributed by Teva Canada Limited)[26] is the first biosimilar of rituximab to become commercially available in Canada. A review was published in November 2019 by the Institut national d'excellence en santé et en services sociaux (INESSS), the health technology assessment body in the province of Quebec.[27] The indications approved by Health Canada do not include severe granulomatosis with polyangiitis (Wegener granulomatosis) or microscopic polyangiitis in adults, and it is unknown whether clinicians will adopt this biosimilar for non-approved indications. Rituxan® is approved by Health Canada for treatment of Wegener granulomatosis, but this indication represents only 1.0% of Rituxan® use in the hospital setting, corresponding to 0.1% of total annual drug expenses (Table 1). Therefore, using a biosimilar of rituximab for this indication would not have a significant impact on annual drug spending, whereas using a biosimilar for non-approved uses in oncology could generate more important savings. Moreover, because of the uncertainty surrounding the amplitude of the price reduction associated with the biosimilar, in our analysis we considered several possible situations, represented by 3 scenarios. For example, every 10% price reduction relative to the reference product rituximab would generate savings according to the extent of uses in the hospital (Table 3).

Limitations

The current analysis was based on data collected for patients who received the reference product (rituximab) in 2016. It is worth mentioning that subsequent validations have shown that the proportion of rituximab used for each indication category has remained stable in the following years, given that no new indications have been approved. However, in the near future, the overall number of doses of rituximab administered intravenously may change, because a subcutaneous formula of rituximab has recently been approved by Health Canada.[28,29] Hence, savings estimated in the current analysis for one specific oncologic indication may be greater than what will be realized following listing of the subcutaneous formulation. The results of our analysis should also be interpreted in the context of each jurisdiction. In particular, if a jurisdiction decides to apply a preferred reimbursement policy to the biosimilar of rituximab only for indications approved by Health Canada, scenario 1 would be applied. Hospital stakeholders and clinicians would then have to decide which part of scenario 2 they would be willing to apply in their hospital. If Rituxan® is completely delisted, scenario 3 would apply, with the biosimilar being used for all indications, whether approved by Health Canada or not. Such a policy could be implemented gradually, with Rituxan therapy continuing for those who are already receiving it and covering the biosimilar only for treatment-naive patients. However, given the nature of the indications and their associated duration of treatment, it seems that almost all patients will be receiving the biosimilar within the 2 years following implementation of the policy. Hence, savings estimated for the first few years will be overestimated. Finally, annual savings in our analysis rely mainly on the fact that, for oncology indications and treatment in the province of Quebec, rituximab must be administered in the hospital setting, with financing by the hospital; as such, the estimated savings would not be generalizable to all other jurisdictions.

CONCLUSION

The use of rituximab is an important aspect of total annual drug expenses for university teaching hospitals. Real-world data from one such hospital show that rituximab is prescribed for several therapeutic indications, but it is not known to what extent clinicians would be willing to prescribe a biosimilar of rituximab for uses that are not approved by Health Canada. The arrival of a biosimilar of rituximab on the Canadian market would generate significant savings. To properly assess the potential savings that this agent might generate in the context of a hospital's limited budget, it seems important to consider all of the indications for which it could be used.

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Rebleeding in Variceal and Nonvariceal Gastrointestinal Bleeds in Cirrhotic Patients Using Vitamin K_1: The LIVER-K Study

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ABSTRACT

Background: Gastroesophageal varices are the most common cause of upper gastrointestinal bleeding (UGIB) in patients with cirrhosis. Vitamin K_1 is commonly administered to patients presenting with UGIB and elevated international normalized ratio, despite limited evidence to support this practice.

Objectives: The primary objective was to describe the incidence of rebleeding within 30 days after vitamin K_1 administration in patients with cirrhosis and UGIB. The secondary objective was to describe prescribing patterns for vitamin K_1.

Methods: This retrospective, descriptive multicentre study involved patients with cirrhosis and UGIB who were admitted to any of the 4 adult acute care hospitals in Calgary, Alberta, from January 1, 2014, to December 31, 2016. Patients were divided into 2 groups: those who received vitamin K_1 and those who did not.

Results: A total of 370 patients met the inclusion criteria, of whom 243 received vitamin K_1 and 127 did not. Baseline characteristics were similar between the groups. Greater proportions of patients in the vitamin K_1 group received transfusions of packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, or prothrombin concentrate during their admissions. There was no significant difference in the duration of octreotide and pantoprazole infusions. Among patients in the vitamin K_1 group, there were more admissions to the intensive care unit and longer lengths of stay. More patients in the no vitamin K_1 group had esophageal varices evident on endoscopy that required endoscopic treatment. Forty of the patients (16.5%) in the vitamin K_1 group and 7 (5.5%) in the no vitamin K_1 group had rebleeding within 30 days of the initial bleed. The median total vitamin K_1 dose administered was 25 mg.

Conclusions: The study results suggest that vitamin K_1 does not reduce the incidence of rebleeding within 30 days of the initial bleed in patients with cirrhosis and UGIB.

Keywords: vitamin K_1, phytonadione, liver cirrhosis, esophageal and gastric varices, gastrointestinal hemorrhage

RÉSUMÉ

Contexte : Les varices œsophagiennes sont la cause la plus fréquente de l'hémorragie gastro-intestinale supérieure (HGIS) parmi les patients atteints de cirrhose. On administre communément de la vitamine K_1 aux patients présentant une HGIS et dont la mesure du rapport international normalisé (RIN) est élevée, malgré le manque de preuves soutenant cette pratique.

Objectifs : L'objectif principal consistait à décrire la fréquence de la reprise du saignement dans les 30 jours après l'administration de la vitamine K_1 à des patients atteints de cirrhose et de HGIS. L'objectif secondaire consistait à décrire les schémas de prescription de la vitamine K_1.

Méthode : Cette étude multicentrique, descriptive et rétrospective comprenait des patients atteints de cirrhose et de HGIS, ayant été admis à n'importe lesquels des quatre hôpitaux de soins actifs pour adultes de Calgary, Alberta, du 1er janvier 2014 au 31 décembre 2016. Les patients étaient répartis en deux groupes : ceux ayant reçu de la vitamine K_1 et ceux n'en ayant pas reçu.

Résultats : Le nombre total de 370 patients correspondait aux critères d'inclusion. Parmi ceux-ci, 243 avaient reçu de la vitamine K_1 et 127 n'en n'avaient pas reçu. Les caractéristiques de base étaient similaires entre les groupes. Un plus grand nombre de patients du groupe « Vitamine K_1 » avaient reçu une transfusion d'un concentré de globules rouges, de plasma frais congelé, de plaquettes, de cryoprécipité ou de concentré de prothrombine au cours de leur séjour hospitalier. On n'a noté aucune différence significative dans la durée des injections de pantoprazole et d'octréotide. Le nombre d'admissions de patients du groupe « Vitamine K_1 » à l'unité de soins intensifs était plus élevé et le séjour de ceux-ci était plus long. L'endoscopie a montré qu'un plus grand nombre de patients du groupe « Sans vitamine K_1 » présentaient des varices œsophagiennes nécessitant un traitement endoscopique. Dans les 30 jours après le saignement initial, quarante (16,5 %) patients du groupe « Vitamine K_1 » et 7 (5,5 %) du groupe « Sans vitamine K_1 » ont subi une nouvelle hémorragie. La dose moyenne totale de vitamine K_1 administrée était de 25 mg.

Conclusions : Les résultats de l'étude tendent à démontrer que la vitamine K_1 ne réduit pas la fréquence de la reprise du saignement dans les 30 jours qui suivent le saignement initial parmi les patients atteints de cirrhose et de HGIS.

Mots-clés : vitamine K_1, phytonadione, cirrhose du foie, varices œsophagiennes et gastriques, hémorragie gastro-intestinale.

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INTRODUCTION

One in 10 Canadians has some form of liver disease.[1] The most common cause of upper gastrointestinal bleeding (UGIB) in patients with cirrhosis is gastroesophageal varices, which are present in nearly 50% of these patients.[2] Variceal hemorrhage occurs at a rate of 10% to 15% per year and depends on the severity of liver disease, the size of varices, and the presence of red wale marks.[2] Patients who recover from a first episode of variceal hemorrhage have a 60% risk of rebleeding in the first year.[2] The mortality rate at 6 weeks after an episode of variceal hemorrhage is 15% to 25%.[2] In addition, coagulopathy in patients with cirrhosis is complex and is affected by numerous factors, including coagulopathic imbalances, infection, endogenous heparinoids, renal failure, endothelial dysfunction, and impaired absorption of fat-soluble vitamins (A, D, E, K).[3,4] As a result, these patients often present with elevated international normalized ratio (INR) and prolonged prothrombin time.[4]

Administration of vitamin K_1 to patients with cirrhosis who present with UGIB is commonly used in clinical practice to improve hemostasis and to reverse potential vitamin K deficiency and INR elevation. Vitamin K_1 acts a cofactor in γ-carboxylation of multiple glutamate residues, allowing for the formation of coagulation factors and binding to γ-carboxylated proteins such as prothrombin; factors VII, IX, and X; and proteins C and S.[4] However, the Canadian Association of Gastroenterology and the American College of Gastroenterology do not mention vitamin K_1 in their guidelines for the treatment of UGIB in patients with cirrhosis.[2-5] In addition, the dose, frequency, and duration of vitamin K_1 administration varies in clinical practice. No randomized controlled trials have examined the benefits or harms of vitamin K_1 in patients with liver disease and UGIB.[6] The primary objective of the current study was to describe the incidence of rebleeding at 30 days in patients with cirrhosis and UGIB who did and did not receive vitamin K_1. The secondary objective was to describe the prescribing patterns for vitamin K_1 administered to patients with cirrhosis and UGIB.

METHODS

Study Design

This was a retrospective, descriptive, multicentre study. Patients with cirrhosis and UGIB admitted to any of the 4 adult acute care hospitals in Calgary, Alberta, from January 1, 2014, to December 31, 2016, were eligible for the study.

Data Sources

A computerized search was conducted using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes within the Data Integration Measurement and Reporting (DIMR) hospital discharge abstract administrative database. Patients were identified by cross-referencing the DIMR list with Sunrise Clinical Manager, the electronic medical record used within the Calgary Zone, which was then used to gather information on demographic characteristics, laboratory values, blood products and medications administered, and discharge information. The provincial Pharmacy Information Network was used to retrieve medication information. Endoscopy reports were obtained from EndoPro (Pentax Medical Company), a database used by the Department of Gastroenterology, Calgary Zone, Alberta Health Services.

Inclusion and Exclusion Criteria

Patients who were 18 years of age or older with a diagnosis of cirrhosis and UGIB, as defined by the ICD-10 codes, were included. Patients whose duration of admission was less than 3 days and those with no electronic discharge summary or endoscopy report were excluded. For patients with multiple admissions during the study period, only the first admission was included in the analysis.

Outcomes

The primary outcome was the incidence of rebleeding within 30 days after the initial bleed, in relation to whether or not vitamin K_1 was administered. This outcome was based on rebleeding that occurred during the index admission, as well as postdischarge UGIB leading to readmission to any of the 4 adult acute care sites within 30 days. Rebleeding rates were compared between patients who and did not receive vitamin K_1. Resolution of the initial bleed was defined as occurring on the date of endoscopy. Rebleeding was defined as a decrease in hemoglobin concentration of more than 20 g/L after endoscopy or bleeding leading to transfusion of 2 or more units of packed red blood cells.[7] The secondary outcome was a description of vitamin K_1 prescribing patterns, including dose, route, frequency, and total number of doses administered.

Patient Characteristics and Data Collection

Demographic data were collected for each patient, including age, sex, weight, and cirrhotic complications and characteristics (previous variceal and nonvariceal UGIB, portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, transjugular intrahepatic portosystemic shunt, portal vein thrombosis, and hepatic encephalopathy). Baseline laboratory values collected included hemoglobin, platelet count, serum creatinine, and INR. The model for end-stage liver disease (MELD) score[8] and the Glasgow-Blatchford bleeding score[9] were calculated. Additional risk factors for bleeding were collected from the discharge summary and Pharmacy Information Network data. Prescriptions for anticoagulants, nonsteroidal anti-inflammatory drugs, antiplatelet agents, nonselective ß-blockers, and proton pump

inhibitors (PPIs) within 180 days before and 30 days after the hospital admission were determined from the Pharmacy Information Network.

Data on admissions to the intensive care unit (ICU), total length of stay, death during the study period, and standard endoscopic treatment and findings were also collected. Endoscopic findings associated with increased risk of rebleeding include high-risk stigmata of peptic ulcer disease, defined as active spurting vessel, nonbleeding visible vessel, or adherent clot.[5] The presence and severity of esophageal varices—where severity was based on the size of the varices and the presence or absence of red colours, as accepted by the US, European, and Asian-Pacific associations for the study of liver disease—were collected.[10] Data on adverse events attributed to vitamin K_1 administration were also collected.

Statistical Analysis

Descriptive statistics were used to characterize the study population. Continuous variables that were normally distributed were described using means and standard deviations, whereas continuous variables that were not normally distributed were described using medians and interquartile ranges (IQRs). Categorical variables were described using frequency counts and proportions. Test of proportions were used to compare proportions between the study groups, and χ^2 tests were used to study correlations between pairs of categorical variables. The Wilcoxon signed-rank test was used to compare medians between 2 groups. Binary logistic regression was used to determine the factors associated with whether or not a patient received vitamin K_1 and to determine the factors associated with rebleeding for the vitamin K_1 subgroup only. Univariate logistic regression was used to determine whether any of these factors were significant. For the final multivariate model, the most parsimonious model was chosen, on the basis of clinical and statistical significance. A *p* value less than 0.05 was considered statistically significant. SPSS software, version 25 (IBM Corporation, Armonk, New York) was used to perform all statistical testing, and 2-sided tests were used for all of the statistical analyses.

RESULTS

A total of 553 patients were eligible for the study (Figure 1), of whom 370 met the inclusion criteria. Of these patients, 243 had received vitamin K_1, and 127 had not received vitamin K_1. Baseline characteristics were similar between the 2 groups; however, a greater proportion of patients in the no vitamin K_1 group had prior portal vein thrombosis, and a greater proportion of this group had a prescription for PPI before admission (Table 1). The proportion of patients with a prescription for nonselective ß-blocker before admission was similar between the 2 groups. Hemoglobin level, INR, and MELD score, were similar on presentation to the hospital.

Greater proportions of patients who had received vitamin K_1 received transfusions of packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, and prothrombin concentrate and received tranexamic acid during the admission (Table 2). There was no statistically significant difference between the groups in terms of the dose, frequency, or duration of IV octreotide and pantoprazole or the duration of antibiotic therapy for manage-

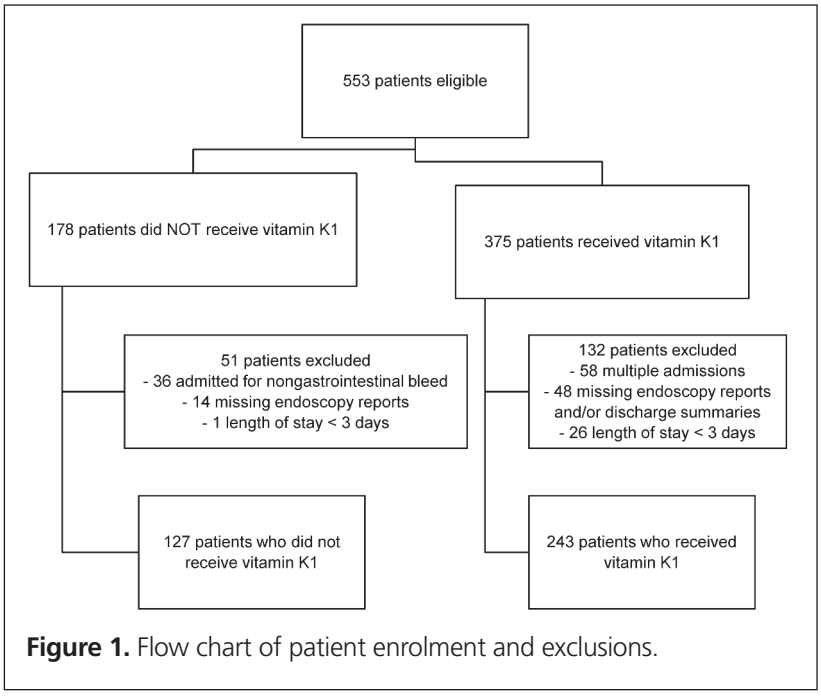

Figure 1. Flow chart of patient enrolment and exclusions.

Table 1. Baseline Characteristics of Patients

Characteristic	Study Group; No. (%) of Patients*		*p* Value
	Vitamin K_1 (*n* = 243)	No Vitamin K_1 (*n* = 127)	
Sex, male	169 (69.5)	78 (61.4)	0.12
Age (years) (mean ± SD)	56.8 ± 11.7	60 ± 8	0.002
Weight (kg) (mean ± SD)†	84 ± 23	79.5 ± 4.6	0.004
Complications of cirrhosis			
Ascites	94 (38.7)	58 (45.7)	0.20
Hepatic encephalopathy	47 (19.3)	25 (19.7)	0.95
Portal hypertensive gastropathy	116 (47.7)	67 (52.8)	0.36
Portal vein thrombosis	11 (4.5)	17 (13.4)	0.002
Previous variceal bleed	31 (12.8)	24 (18.9)	0.12
Previous nonvariceal bleed	13 (5.3)	11 (8.7)	0.22
Spontaneous bacterial peritonitis	10 (4.1)	4 (3.1)	0.64
Transjugular intrahepatic portosystemic shunt	3 (1.2)	4 (3.1)	0.20
Blood components			
Hemoglobin (g/L) (mean ± SD)	97 ± 28.1	94 ± 25.1	0.28
Hemoglobin < 70 g/L	53 (21.8)	23 (18.1)	0.40
Platelet count (× 10^9/L) (median and IQR)	106 (73–161)	126 (87–174)	0.019
Platelets < 50 × 10^9/L	22 (9.1)	10 (7.9)	0.70
Serum creatinine (µmol/L) (median and IQR)	81 (59–130)	73 (55–109)	0.019
INR (mean ± SD)	1.9 ± 0.9	1.3 ± 0.3	0.99
MELD score (mean ± SD)	19.4 ± 7.8	13 ± 5	0.98
Glasgow-Blatchford bleeding score (mean ± SD)‡	9.5 ± 4	11.2 ± 4.1	< 0.001
Home medications			
Warfarin	9 (3.7)	1 (0.8)	0.10
Low-molecular-weight heparin	4 (1.6)	6 (4.7)	0.08
Fondaparinux	0	1 (0.8)	0.17
Direct oral anticoagulant	3 (1.2)	0 0.21	
Clopidogrel, prasugrel, or ticagrelor	1 (0.4)	3 (2.4)	0.08
NSAID	45 (18.5)	25 (19.7)	0.79
Proton pump inhibitor	87 (35.8)	64 (50.4)	0.007
Nonselective ß-blocker	64 (26.3)	39 (30.7)	0.37
ICU admission	65 (26.7)	14 (11.0)	< 0.001
Length of stay (days) (median and IQR)	10 (5–19)	5 (4–9)	< 0.001

ICU = intensive care unit, INR = international normalized ratio, IQR = interquartile range, MELD = model for end-stage liver disease (calculated from serum creatinine, INR, and total bilirubin), NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.
*Except where indicated otherwise.
†Weight was not documented for 26 patients in the group that received vitamin K_1 and 16 patients in the group that did not receive vitamin K_1.
‡Derived from urea, hemoglobin, systolic blood pressure, heart rate, sex, presence of melena, history of recent endoscopy, recent syncope, and presence of heart failure and/or liver disease.

ment of acute UGIB (data not shown). More patients in the vitamin K_1 group had high-risk stigmata evident on endoscopy that required endoscopic treatment. A greater proportion of patients in the no vitamin K_1 group had esophageal varices evident on endoscopy that required endoscopic treatment (Table 2). Two patients who had received vitamin K_1 and 4 patients who had not received vitamin K_1 were positive for *Helicobacter pylori* on biopsy. In addition, 13 patients who had received vitamin K_1 and 5 patients who had not received vitamin K_1 received empiric therapy for eradication of *H. pylori* ($p = 0.55$).

There was an approximate 2-fold increase in frequency of ICU admission (26.7% versus 11%, $p < 0.001$) and length of stay (10 days versus 5 days, $p < 0.001$) for patients in the vitamin K_1 group. Significantly more patients in the no vitamin K_1 group than in the vitamin K_1 group were given a prescription for nonselective ß-blocker upon discharge (84 [66.1%] of 127 versus 114 [46.9%] of 243; $p < 0.001$). More patients in the vitamin K_1 group than in the no vitamin K_1 group were given a prescription for twice-daily oral PPI upon hospital discharge (68.7% versus 58.3%; $p = 0.045$). There was no significant difference in the proportion of patients for whom once-daily oral PPI was prescribed (38 [15.6%] of 243 who receive vitamin K_1 versus 30 [23.6%] of 127 who did not received vitamin K_1; $p = 0.06$).

A significantly greater proportion of patients in the vitamin K_1 group had rebleeding within 30 days after the initial bleed ($p = 0.003$) (Figure 2). In particular, the rate of rebleeding during

Table 2. Management of Upper Gastrointestinal Bleeding (UGIB) and Endoscopy Results

Variable	Study Group; No. (%) of Patients		*p* Value
	Vitamin K_1 (*n* = 243)	No Vitamin K_1 (*n* = 127)	
Management of UGIB			
Received packed red blood cells	164 (67.5)	71 (55.9)	0.028
Received fresh frozen plasma	133 (54.7)	14 (11.0)	< 0.001
Received platelets	59 (24.3)	8 (6.3)	< 0.001
Received cryoprecipitate	16 (6.6)	2 (1.6)	< 0.001
Received 4-factor prothrombin concentrate	10 (4.1)	0	0.02
Received factor VII	1 (0.4)	0	0.47
Received tranexamic acid	21 (8.6)	3 (2.4)	0.020
Endoscopy findings			
Active spurting vessel	11 (4.5)	2 (1.6)	0.14
Nonbleeding visible vessel	7 (2.9)	5 (3.9)	0.59
Adherent clot	14 (5.8)	2 (1.6)	0.06
Patients with high-risk stigmata requiring endoscopic treatment*	14 (5.8)	5 (3.9)	0.45
Esophageal varices	145 (59.7)	101 (79.5)	< 0.001
Gastric varices	14 (5.8)	5 (3.9)	0.45
Portal hypertensive gastropathy	28 (11.5)	17 (13.4)	0.60
Gastroesophageal varices requiring treatment	75 (30.9)	58 (45.7)	0.005
Other causes of bleeding†	31 (12.8)	24 (18.9)	0.12

IQR = interquartile range.
*Active spurting vessel, nonbleeding visible vessel, and/or adherent clot.
†Other causes of bleeding included (but were not limited to) esophagitis, erosive gastroduodenopathy, gastric antral vascular ectasia, malignancy, Mallory-Weiss tear, angiodysplasia, Dieulafoy lesion, telangectasia.

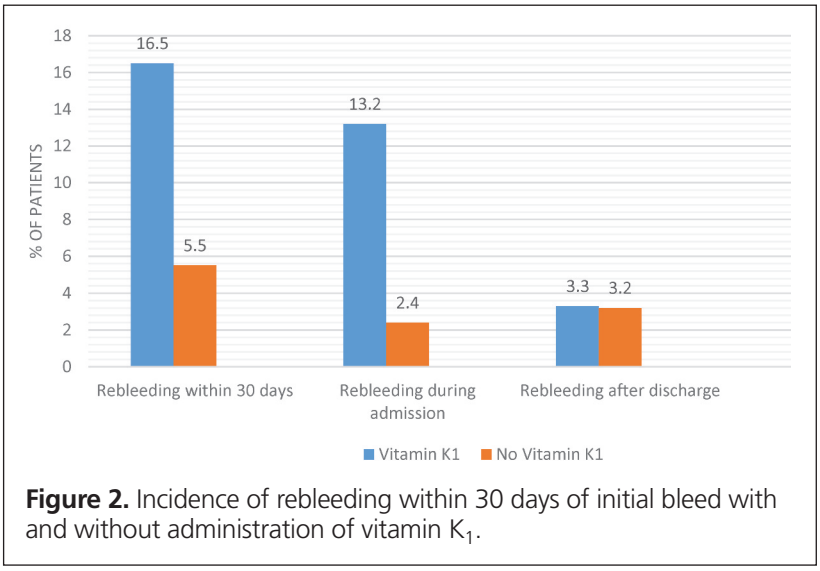

Figure 2. Incidence of rebleeding within 30 days of initial bleed with and without administration of vitamin K_1.

the index hospital admission was 13.2% (32/243) in the vitamin K_1 group and 2.4% (3/127) in the no vitamin K_1 group (p = 0.038). Because only a few patients in the no vitamin K_1 group had rebleeding, we were unable to complete the regression analysis to determine the impact of vitamin K_1 on rebleeding in cirrhotic patients presenting with UGIB. However, length of stay, ICU admission, and higher values for the Glasgow-Blatchford bleeding score were more likely to be associated with rebleeding within the vitamin K_1 group (Table 3). In the comparative regression analysis of vitamin K_1 versus no vitamin K_1, INR was more likely than other factors considered in the analysis to be associated with increased risk of rebleeding (Table 4).

Overall, 123 (33.2%) of the 370 patients died during the study period. In particular, 59 (24.3%) of the 243 patients in the vitamin K_1 group died during the index admission, as compared with 2 (1.6%) of the 127 patients in the no vitamin K_1 group (p < 0.001). Death was most commonly attributed to end-stage liver disease.

The dose of vitamin K_1 most commonly prescribed was 10 mg, for IV or oral administration (Table 5). The median

Table 3. Multivariate Analysis of Rebleeding among Patients Who Received Vitamin K_1

Variable	OR (95% CI)		*p* Value
High-risk stigmata on endoscopy*	1.416	(0.354–5.667)	0.62
INR	1.102	(0.497–2.443)	0.81
MELD score	1.024	(0.933–1.124)	0.62
Glasgow-Blatchford bleeding score	0.787	(0.674–0.919)	0.003
ICU admission	4.604	(1.330–15.939)	0.016
Length of stay	1.026	(1.007–1.046)	0.007
Esophageal varices	0.561	(0.173–1.821)	0.34
Anticoagulation before admission	0.691	(0.070–6.790)	0.75
Nonselective ß-blocker	0.358	(0.106–1.207)	0.10
Proton pump inhibitor	1.949	(0.461–8.237)	0.36

CI = confidence interval, ICU = intensive care unit, INR = international normalized ratio, MELD = model for end-stage liver disease score.
*Active spurting vessels, nonbleeding visible vessels, and/or adherent clot.

Table 4. Multivariate Analysis of Rebleeding among Patients Who Did and Did Not Receive Vitamin K_1

Variable	OR (95% CI)		*p* Value
Esophageal varices	0.590	(0.153–2.275)	0.44
High-risk stigmata on endoscopy*	4.515	(0.526–38.745)	0.17
Anticoagulation before admission	1.333	(0.165–10.759)	0.79
Nonselective ß-blocker	1.109	(0.288–4.278)	0.88
Proton pump inhibitor	1.204	(0.255–5.688)	0.81
ICU admission	2.956	(0.516–16.950)	0.22
Length of stay	1.035	(0.974–1.101)	0.27
INR	4.621	(1.587–7.655)	0.003
MELD score	0.998	(0.872–1.144)	0.98
Glasgow-Blatchford bleeding score	0.885	(0.751–1.043)	0.14

CI = confidence interval, ICU = intensive care unit, INR = international normalized ratio, MELD = model for end-stage liver disease score.
*Active spurting vessels, nonbleeding visible vessels, and/or adherent clot

Table 5. Summary of Vitamin K_1 Prescribing Patterns (*n* = 1079 Doses)

Variable	Result
Smallest dose prescribed (mg)	2.5
Largest dose prescribed (mg)	20
Dose (mg) (mean ± SD)	10 ± 0
No. (%) 10-mg doses prescribed	787 (72.9)
Cumulative dose per patient (mg) (median and IQR)	25 (10–40)
Cumulative doses received per patient (median and IQR)*	3 (1–5)*
No. (%) of doses by route of administration	
IV	624 (57.8)
Oral	422 (39.1)
Intramuscular	3 (0.3)
Subcutaneous	30 (2.8)

*Eighty-nine patients received only a single dose of vitamin K_1.

cumulative vitamin K_1 dose was 25 mg administered over 3 days. Eighty-nine (36.6%) of the 243 patients in the vitamin K_1 group received a single dose. No adverse effects of vitamin K_1 were reported.

DISCUSSION

The administration of vitamin K_1 for acute management of UGIB in patients with cirrhosis is common practice, despite limited supporting evidence. Patients with chronic liver disease have altered hemostasis, because liver disease profoundly affects coagulation through abnormalities in platelet-vessel interactions, thrombin generation and inhibition, clotting factor production, and clot dissolution.[11,12] Underlying conditions that increase the risk of bleeding in patients with cirrhosis include portal hypertension, endothelial dysfunction, bacterial infection, thrombocytopenia, development of endogenous heparin-like

substances, and renal failure.[11,13] In the current study, there was no significant difference in portal hypertensive gastropathy, renal function, or duration of prophylactic antibiotic therapy. The patients who received vitamin K_1 had more severe thrombocytopenia and received significantly more platelet transfusions. A platelet count as low as 50–60 × 10^9/L in patients with cirrhosis is usually sufficient to preserve thrombin generation, and counts above 100 × 10^9/L show little extra benefit relative to controls.[11,12] In the current study, there was no significant difference between groups in the proportion of patients with platelet count less than 50 × 10^9/L. Patients with cirrhosis have increased levels of von Willebrand factor, which increases the adhesive capacity of platelets, resulting in increased effectiveness of the limited number of platelets.[4,11,12]

The patients who received vitamin K_1 appeared to have greater clinical instability than those who did not receive vitamin K_1, as demonstrated by the statistically significant difference in ICU admissions and the increased length of stay. This greater clinical instability is also indicated by the increased proportions of patients who received packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, or prothrombin concentrate during their admission. Patients who received vitamin K_1 also received more tranexamic acid to control UGIB, which suggests that they exhibited greater coagulopathy than the patients who did not receive vitamin K_1.[14] We propose that vitamin K_1 was administered to those with more advanced liver disease and more severe, life-threatening hemorrhage. Indeed, a greater proportion of patients in the vitamin K_1 group than the no vitamin K_1 group died before hospital discharge due to end-stage liver disease.

Our study showed that the greater the Glasgow-Blatchford bleeding score, the greater the risk of rebleeding in patients who received vitamin K_1. This bleeding score is derived from urea, hemoglobin, systolic blood pressure, heart rate, sex, presence of melena, history of recent endoscopy, recent syncope, and presence of heart failure and/or liver disease. It is a formal risk assessment tool for UGIB to identify patients who require urgent medical or endoscopic therapy (i.e., score > 2),[15,16] although it has not been validated to assess the risk of rebleeding in patients with cirrhosis and UGIB. The score predicted urgent intervention for all of the included patients. Despite the statistically significant difference between the 2 groups, the Glasgow-Blatchford bleeding score did not influence rebleeding, as shown by the results of the regression analysis. This result may have been influenced by the low number of patients with rebleeding in the no vitamin K_1 group.

Our study also suggested that the greater the INR, the greater the risk of rebleeding in patients with cirrhosis presenting with UGIB. Among patients in the vitamin K_1, the INR was 46% higher than among those in the no vitamin K_1 group, although the difference was not statistically significant. INR is a measure of vitamin K_1–dependent clotting factors that was originally developed in the early 1980s for standardization of therapeutic anticoagulation with vitamin K antagonists in healthy volunteers. However, it has not been validated for patients with chronic liver disease.[11,12,17] In patients with cirrhosis, coagulopathy is complex, and their elevated INR may be a result of multiple factors, including decreased synthesis of clotting factors due to intrinsic hepatic impairment, rather than vitamin K_1 deficiency. INR is not a predictor of rebleeding in nonvariceal UGIB.[18] Nevertheless, in practice, the INR is typically measured for patients with cirrhosis who present with UGIB, and those with elevated INR values often receive parenteral vitamin K_1.[4] Vitamin K_1 can reduce INR by 0.2 to 0.3 in some patients with cirrhosis-associated coagulopathy; however, those with more advanced liver disease (MELD score > 30) rarely experience a reduction in INR with such treatment.[3,19]

Nonselective ß-blockers reduce portal pressure and are used in the primary and secondary prophylaxis of variceal hemorrhage.[20] The goal of therapy is to achieve a heart rate of 55 to 60 beats/min, while maintaining systolic blood pressure above 90 mm Hg.[2] In the current study, we were unable to investigate whether patients achieved this goal. There is a clinical window within which ß-blockers are associated with higher rates of survival. The clinical window opens when moderate to large esophageal varices develop, and patients may present with or without variceal bleeding.[20] The clinical window closes when refractory ascites, hypotension (systolic blood pressure below 100 mm Hg or mean arterial pressure below 82 mm Hg), serum sodium below 120 mmol/L, acute kidney injury, hepatorenal syndrome, spontaneous bacterial peritonitis, sepsis, or severe alcoholic hepatitis develops, leading to unfavourable hemodynamic effects in advanced cirrhosis.[2,20] Relative to baseline, there were increases of 78% in the use of nonselective ß-blockers in the vitamin K_1 group and 115% in the no vitamin K_1 group. Nonselective ß-blockers reduce the risk of recurrent variceal bleeding from 63% to 42% (number needed to treat 5).[21] This may have contributed to the lower number of recurrent bleeds in the no vitamin K_1 group.

The doses of vitamin K_1 commonly administered in clinical practice range from 0.5 to 10 mg daily, but limited evidence exists concerning the route or frequency of administration. The most common dose of vitamin K_1 prescribed in the current study was 10 mg, with a median cumulative dose of 25 mg. Most patients received 3 doses. The most common route of administration was oral or parenteral. These data are similar to the dose, route of administration, and frequency of administration that have been described previously.[3,4,19]

Selection bias may have existed, given the differences in baseline characteristics, endoscopic results, and management of UGIB between the 2 groups. This is a limitation of the study design, given that this was a retrospective, descriptive study from which we cannot explicitly derive treatment effect.

CONCLUSION

Despite the lack of evidence to support the efficacy of vitamin K_1 to reduce the risk of rebleeding in patients with cirrhosis and UGIB, vitamin K_1 administration is common. This descriptive study suggests that vitamin K_1 does not reduce the incidence of rebleeding within 30 days after an initial bleed in patients with cirrhosis and UGIB. Because the study was retrospective and descriptive, we cannot explicitly conclude a treatment effect. Patients who received vitamin K_1 were more likely than those who did not receive vitamin K_1 to be clinically unstable. This difference in clinical stability may have resulted in the observed differences in pharmacological management at discharge, which in turn may have influenced rebleeding. Prospective randomized studies are needed to determine the efficacy and safety of vitamin K_1 for patients with hepatic cirrhosis and UGIB.

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Analyse de minimisation de coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique en établissement de santé

par Annaelle Soubieux, Caroline Plante, Johann-François Ouellette-Frève, Audrey Chouinard et Jean-François Bussières

RÉSUMÉ

Contexte : Il existe de nombreuses stratégies visant à réduire les risques d'exposition professionnelle aux médicaments dangereux qui pèsent sur les travailleurs du domaine de la santé, dont les systèmes utilisés pour la préparation et l'administration des médicaments.

Objectif : L'objectif principal était de comparer le coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique par voie intraveineuse (IV) dans un établissement de santé canadien pour adultes entre un système classique et un autre intégrant un système clos de transfert de médicament (SCTM).

Méthode : Il s'agit d'une analyse de minimisation de coûts. La perspective adoptée est celle d'un établissement de santé universitaire type. L'évaluation ne porte que sur le coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique IV. Il n'est pas nécessaire de procéder à l'actualisation des coûts. Nous avons déterminé 12 scénarios comportant certaines des 11 étapes possibles de la préparation et de l'administration d'une dose IV d'antinéoplasique.

Résultats : Le coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique varie entre 9,89 $ et 22,37 $ la dose pour le système classique et entre 12,34 $ et 64,19 $ la dose pour les systèmes intégrant un SCTM. Le surcoût moyen annuel des systèmes intégrant un SCTM est de 1,63 à 3,15 fois supérieur par rapport au système classique et il représente une dépense annuelle additionnelle allant de 363 566 $ à 1 238 072 $ par année pour un établissement de santé type pour adultes.

Conclusion : Cette analyse de minimisation de coûts présente des données originales entourant la préparation et l'administration IV d'antinéoplasiques. Compte tenu des coûts importants associés à la préparation et l'administration des antinéoplasiques, les décideurs devraient mener des analyses complètes des coûts et des conséquences afin d'assurer une prise de décision éclairée.

Mots-clés : médicaments dangereux, préparation, administration, système clos de transfert de médicament

ABSTRACT

Background: Many strategies aim to reduce the risk of work-related exposure to hazardous drugs for health care workers; these strategies include the use of specific systems to prepare and administer these drugs.

Objective: To compare the cost of supplies used for preparing and administering one IV dose of antineoplastic in an adult health care facility in Canada between the traditional approach and one using a closed-system drug transfer device (CSTD).

Method: This study was a cost reduction analysis conducted from the perspective of a typical university health care facility. The assessment focused only on the cost of supplies used to prepare and administer one IV dose of antineoplastic. It was not necessary to account for discounting. We developed 12 scenarios involving some of the 11 possible steps in preparing and administering one IV dose of antineoplastic.

Results: The cost of supplies used to prepare and administer one IV dose of antineoplastic ranged between $9.89 and $22.37 per dose with the classical system, and between $12.34 and $64.19 per dose for systems involving a CSTD. The annual average extra cost of systems involving a CSTD was 1.63 to 3.15 higher than the cost with the classical system and represents extra spending of between $363 566 and $1 238 072 each year for a typical adult health care institution.

Conclusion: This cost reduction analysis presents original data relating to the preparation and administration of IV antineoplastics. Given the significant costs associated with preparing and administering antineoplastic drugs, decision-makers should perform a thorough analysis of costs and consequences to allow informed decisions to be made.

Keywords: hazardous drug, preparation, administration, closed-system drug transfer device

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INTRODUCTION

Depuis plusieurs années déjà, on reconnaît le danger que courent les travailleurs de la santé exposés aux médicaments dangereux[1]. Ces derniers sont définis par le National Institute of Occupational Safety and Health (NIOSH) comme comportant une des caractéristiques suivantes : cancérogène, tératogène, génotoxique, toxique pour la reproduction, toxique pour un organe à faible dose. Ils sont catégorisés en trois groupes (groupe 1 : antinéoplasiques, groupe 2 : les médicaments non antinéoplasiques répondant à au moins une des caractéristiques du NIOSH, groupe 3 : représentant un risque pour la reproduction)[2]. Les travailleurs de la santé peuvent être exposés à ces risques à différentes étapes du circuit du médicament, tant à la pharmacie que dans les zones de traitement des patients[3–5].

Plusieurs lignes directrices encadrent la préparation et l'administration des antinéoplasiques et des autres médicaments dangereux afin de diminuer les risques d'exposition des travailleurs. Elles comportent différentes stratégies, dont le choix de fournitures destinées à la préparation et à l'administration des médicaments[1,6-13].

Plusieurs fournitures sont nécessaires aux différentes étapes du circuit du médicament, dont des systèmes classiques ou des systèmes intégrant un système clos de transfert de médicaments (SCTM). Les SCTM sont des « dispositifs de transfert de médicaments qui empêchent mécaniquement le transfert de contaminants de l'environnement dans le système et la fuite du médicament dangereux ou des concentrations de vapeurs dangereuses vers l'extérieur du système »[1]. Les SCTM diffèrent des systèmes classiques en permettant une connexion sèche lors des transferts de médicaments (p. ex. adaptation aux fioles, aux seringues, aux tubulures). Ils empêcheraient ainsi la formation d'aérosols ou de gouttelettes de médicaments dangereux et protégeraient mieux le personnel des expositions à ces médicaments. Il n'existe pas de protocole universel d'évaluation de l'efficacité des SCTM[14]. Cependant, vu le risque d'exposition et de contamination croisée, quelques sociétés savantes recommandent l'utilisation de SCTM pour la préparation et l'administration des médicaments dangereux[6,10].

Certaines études ont démontré des réductions de contamination des surfaces à la suite de l'implantation de SCTM à la pharmacie[15-19]. Toutefois, une méta-analyse du groupe Cochrane dit qu'à « l'heure actuelle, aucune conclusion définitive ne peut être tirée quant à l'effet des SCTM associés à une manipulation sans danger par rapport à une manipulation sans danger sans SCTM en raison de preuves de très faible qualité fournies par les principales études évaluées. Des essais randomisés, contrôlés et multicentriques sont réalisables en fonction de la proportion de personnes exposées. Les futures études devraient également évaluer l'exposition à une sélection pertinente de médicaments dangereux utilisés à l'hôpital et mesurer les effets directs sur la santé à court terme »[20]. Comme le soulignent les auteurs de la revue Cochrane, une série chronologique interrompue permettrait une évaluation dans un contexte réel en utilisant un protocole de recherche quasi expérimental.

Il existe en outre très peu d'études économiques portant sur les coûts associés à la préparation et à l'administration des doses d'antinéoplasiques avec des systèmes intégrant des SCTM[21-23]. Compte tenu des différents types de SCTM disponibles, des coûts additionnels associés à l'utilisation de ces fournitures spécifiques et des ressources disponibles en santé, il nous semble utile de comparer le coût des fournitures utilisées pour la préparation et l'administration de doses d'antinéoplasiques en établissement de santé.

MÉTHODE

Type d'évaluation

Il s'agit d'une analyse de minimisation de coûts. Les données sont rapportées selon les critères CHEERS[24] et les lignes directrices de l'évaluation économique des technologies de la santé[25].

Objectif

L'objectif principal était de calculer le coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique avec un système classique et un système intégrant un SCTM. L'objectif secondaire était de comparer le coût d'un système classique à celui d'un sytème intégrant différents SCTM disponibles au Canada et d'estimer le coût annuel moyen dans un établissement de santé universitaire type.

Population cible

L'analyse cible les fournitures utilisées pour la préparation et l'administration de doses d'antinéoplasiques par voie IV en établissement de santé pour une patientèle adulte (≥ 18 ans).

Perspective

La perspective retenue est celle de l'établissement de santé universitaire type.

Comparateur

Il existe différentes techniques de préparation et d'administration des médicaments dangereux, qui nécessitent des fournitures différentes (p. ex. purge de la tubulure à la pharmacie ou dans les services de soins, arbres d'administration différents selon les établissements de santé). Dans cette étude, nous avons choisi d'analyser les systèmes classiques et les systèmes intégrant un SCTM pour la préparation et l'administration de doses d'antinéoplasiques en tenant compte des exigences en vigueur[11,13], des recommandations des membres du groupe d'experts sur les médicaments dangereux de l'ASSTSAS et d'observations directes. Nous avons déterminé les SCTM disponibles au Canada en date du 1er juillet 2018.

Horizon temporel

Il s'agit d'une analyse transversale des coûts en date du 1er septembre 2018.

Actualisation

L'évaluation ne porte que sur le coût des fournitures utilisées pour la préparation et l'administration d'une dose d'antinéoplasique IV. Il n'est pas nécessaire de procéder à l'actualisation des coûts.

Modélisation des scénarios de préparation et d'administration

Il existe différentes options pour préparer et administrer un médicament dangereux. Les fioles peuvent avoir des diamètres différents, le médicament peut être une poudre à reconstituer ou une solution prête à l'emploi. Les médicaments dangereux peuvent être administrés en seringues ou en sacs et le rinçage peut être différent selon les habitudes de chaque établissement de santé (p. ex. rétrograde ou à partir d'une seringue de rinçage). En fonction de ces différents choix, les fournitures à utiliser sont différentes. Nous avons ainsi déterminé 12 scénarios pouvant inclure certaines des 11 étapes possibles de la préparation et de l'administration d'une dose IV d'antinéoplasique (tableau 1). Ces scénarios découlent des caractéristiques des contenants commerciaux de médicaments disponibles au Canada, des différentes fournitures disponibles au Canada, des protocoles et procédures cliniques et de 11 prémisses :

1. *Diamètre des fioles* — Le diamètre varie entre 13 mm, 20 mm et 28 mm; le diamètre des fioles peut faire varier les fournitures utilisées (p. ex. adaptateurs de fioles de taille différente pour la préparation); seuls les contenants de 13 et 20 mm ont été retenus (les établissements de santé sondés n'utilisent pas ceux de 28 mm).
2. *Fiole utilisée par dose* — Les doses varient pour plusieurs raisons (p. ex. indication, poids, surface corporelle, état clinique, protocole); nous avons considéré qu'une seule fiole par dose était utilisée (soit, pour un patient). Une fiole préparée = une dose.
3. *Préparation à partir d'une fiole de 13 mm* — Il n'existe pas d'adaptateur classique (spike) pour le prélèvement de doses dans les fioles de 13 mm; il en existe toutefois pour les SCTM. Une aiguille a été retenue pour le prélèvement d'une dose dans le système classique et un adaptateur pour le système intégrant un SCTM.
4. *Préparation à partir d'une fiole de 20 mm* — Un adaptateur classique ou SCTM a été retenu pour le prélèvement d'une dose.
5. *Préparation de la dose* — Une seringue de 10 mL a été retenue pour la préparation de la dose.
6. *Amorçage de la tubulure à la pharmacie* — L'amorçage était effectué à la pharmacie.
7. *SCTM – adaptateur pour la dilution / le prélèvement à partir d'une fiole* — Nous avons retenu un adaptateur avec un ballon et un adaptateur sans ballon, lorsque cela était possible.
8. *SCTM – adaptateur avec une seringue « classique »* — Nous avons retenu, en fonction de la disponibilité, l'adaptateur avec une seringue « classique » et non avec une seringue intégrée (dispositif SCTM fusionné avec une seringue spécifique).

Tableau 1. Douze scénarios pour la préparation et l'administration d'une dose intraveineuse d'antinéoplasique dans un établissement de santé québécois

	Étapes										
	Diluer / prélever				Compléter le condition-nement de la seringue (contenant final) (étape 5)	Injecter le contenu dans un contenant final (sac) (étape 6)	Relier et administrer le contenant final au patient (sac ou seringue)		Retirer le contenant final du patient		
Scénario	Poudre 13 mm (étape 1)	Poudre 20 mm (étape 2)	Solution 13 mm (étape 3)	Solution 20 mm (étape 4)			Seringue (étape 7)	Sac (étape 8)	Seringue (étape 9)	Sac rincé en rétrograde (étape 10)	Sac rincé avec une seringue (étape 11)
1	×				×		×		×		
2		×			×		×		×		
3			×		×		×		×		
4				×	×		×		×		
5	×					×		×		×	
6	×					×		×			×
7		×				×		×		×	
8		×				×		×			×
9			×			×		×		×	
10			×			×		×			×
11				×		×		×		×	
12				×		×		×			×

9. *SCTM – adaptateur avec une tubulure « classique »* — Nous avons retenu l'adaptateur (bag spike) avec l'utilisation de tubulure « classique » et non avec une tubulure intégrée (dispositif SCTM fusionné avec une une seringue spécifique).
10. *Administration de la dose – dispositifs* — Aucune aiguille n'a été utilisée pour le couplage du contenant final et de la tubulure au patient.
11. *Rinçage après l'administration* — Le rinçage avec injection d'une solution compatible avec une seringue et une aiguille pour le système classique ne semblait pas sécuritaire. Tous les rinçages étaient effectués de manière rétrograde pour le système classique. Le rinçage était effectué en injectant une solution compatible directement dans le sac d'antinéoplasique avec une seringue intégrant un SCTM ou de manière rétrograde pour les systèmes intégrant un SCTM.

Modélisation du coût annuel

Trois chefs de département de pharmacie de centres hospitaliers universitaires pour adultes au Québec ont été sondés sur les données de la consommation et les méthodes d'administration de toutes les fioles d'antinéoplasiques utilisées pour la préparation et l'administration IV de doses pendant l'exercice financier de 2017-2018. Les établissements choisis ont un volume important de préparations de médicaments dangereux. Ils sont représentatifs des centres universitaires pour adultes du Québec. La consommation moyenne de ces établissements a servi à estimer les coûts moyens par année et par dose de préparation et d'administration d'antinéoplasique IV dans un établissement de santé universitaire type.

Efficacité clinique

Aux fins de notre analyse, tous les SCTM ont été considérés équivalents entre eux en termes d'efficacité.

Mesure et évaluation de la santé

Notre étude de minimisation de coûts n'a pas tenu compte des retombées potentielles de l'utilisation des différentes fournitures considérées sur la santé des travailleurs, compte tenu de l'absence de preuves de leur effet sur la santé[20].

Utilisation et coût des ressources

L'étude a porté sur les coûts d'acquisition des fournitures utilisées spécifiquement pour la préparation et l'administration de dose d'antinéoplasique par voie IV. Toutefois, les coûts d'acquisition de certains produits complémentaires, similaires entre les SCTM et les systèmes classiques, n'ont pas été pris en compte (p. ex. diluants, solutés primaires, secondaires, contenant final utilisé pour le médicament antinéoplasique à moins qu'il ne s'agisse de la seringue utilisée pour la préparation) dont les choix varient selon les pratiques de chaque établissement. Les coûts d'incinération ont été pris en compte car les SCTM sont des dispositifs volumineux. Les coûts d'aménagement (p. ex. locaux), de formation, de gestion (p. ex. approvisionnement), de temps de manipulation par le personnel de la pharmacie et le personnel soignant, de formation ou de certification du personnel n'ont pas été évalués.

Les coûts d'acquisition des fournitures pour le système classique étaient ceux provenant de l'entente d'approvisionnement en commun des fabricants à contrat avec SigmaSanté (groupement d'achat des hôpitaux Québécois) en date du 1/9/2018, tandis que les coûts des SCTM ont été fournis par écrit par les fabricants selon les prix en vigueur au moment de la demande. Les fabricants ont été prévenus que les coûts seraient publiés et ils ont signé un consentement.

Les coûts d'incinération ($ CA/kg) en date du 1er septembre 2018 ont également été pris en compte.

Tous les prix sont en dollars canadiens ($ CA).

Analyse

Dans un *premier temps*, le profil des coûts d'acquisition des fournitures retenues pour la préparation et l'administration d'antinéoplasiques a été établi par système (chaque SCTM et classique). Les fournitures ont été pesées sans emballage et sans liquide à l'intérieur pour permettre le calcul du coût d'incinération. À partir de ces coûts et des scénarios établis, les investigateurs ont calculé le coût et le poids par dose pour la préparation et l'administration d'antinéoplasique par le système.

Dans un *deuxième temps*, un sondage effectué auprès des trois chefs de département de pharmacie a servi à l'élaboration du profil d'un établissement universitaire type. Puis les investigateurs ont procédé au calcul du nombre total moyen de fioles utilisées par établissement et par année. Ils ont également quantifié la proportion moyenne de fioles par diamètre et la proportion moyenne de fioles destinées à des doses administrées en seringues ou en sacs. Ces données ont permis d'établir la proportion de chacun des 12 scénarios applicables à un établissement type pour adultes.

Dans *un troisième temps*, l'estimation du coût annuel des fournitures par système pour un établissement type donné a pris en considération le coût par dose de chaque scénario en fonction des proportions du profil de l'établissement universitaire type. Le calcul du coût moyen par dose a été basé sur le coût annuel par système, soit en divisant le coût annuel par système par le nombre moyen de doses par année de l'établissement universitaire type. De plus, le calcul du surcoût des systèmes intégrant un SCTM par rapport au système classique résulte de la division du coût annuel estimé du système intégrant un SCTM par le coût annuel estimé du système classique. Compte tenu que le rinçage avec injection d'une solution compatible à l'aide d'une seringue et d'une aiguille n'est pas jugé sécuritaire pour le système classique, tous les surcoûts ont été calculés en divisant le coût annuel estimé

du système intégrant un SCTM par le coût annuel estimé du système classique avec rinçage rétrograde.

Dans *un quatrième* temps, l'estimation du poids annuel des fournitures par système pour un établissement universitaire type donné résulte du poids par dose de chaque scénario en fonction des proportions du profil d'établissement universitaire type. Le coût moyen annuel d'incinération par système provient de la multiplication de ce poids annuel moyen par le coût de l'incinération.

Incertitude

Bien que les fournitures utilisées pour la préparation et l'administration de doses d'antinéoplasiques soient jetables, elles peuvent néanmoins être réutilisées (p. ex. l'adaptateur de fiole peut servir à prélever la dose supplémentaire d'un patient, la tubulure peut être installée, selon les pratiques de l'établissement, pour une période pouvant aller de 24 à 96 heures) lorsque cela est applicable. Une analyse complémentaire a permis de tenir compte de la préparation et de l'administration d'une 2e et d'une 3e dose en réutilisant les fournitures nécessaires, lorsque cela était possible.

Les investigateurs ont en outre procédé au calcul des statistiques descriptives (moyenne, écart-type).

RÉSULTATS

Comparateur

Sept systèmes intégrant des SCTM provenant de quatre fabricants ont été déterminés comme étant disponibles sur le marché canadien en date du 1er septembre 2018 : Phaseal, Phaseal Optima et Texium (Becton Dickinson), Chemoclave et Chemolock (ICU Medical), Equashield (Equashield) et Onguard (B. Braun). Les sept systèmes intégrant des SCTM ont été comparés au système classique défini pour l'étude.

Coût de préparation et d'administration d'une dose d'antinéoplasique dans un établissement de santé et comparaison des coûts selon les SCTM évalués

L'annexe 1 (disponible au https://www.cjhp-oline.ca/index.php/cjhp/issue/view/195/showToc) présente le coût et le poids des fournitures retenues pour la préparation et l'administration d'une dose IV d'antinéoplasique en établissement de santé par un système classique. Certaines de ces fournitures conviennent également aux systèmes intégrant un SCTM (p. ex. tubulures, seringues).

L'annexe 2 (disponible au https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc) présente le coût des fournitures retenues pour la préparation et l'administration par un système intégrant un SCTM d'une dose IV d'antinéoplasique en établissement de santé.

En ce qui concerne le système classique, le coût des fournitures de préparation et d'administration d'une dose IV d'antinéoplasique variait entre 9,89 $ et 22,37 $ la dose selon les 12 scénarios (annexes 3 et 4, disponibles au https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc).

En ce qui concerne le système intégrant un SCTM, le coût des fournitures de préparation et d'administration d'une dose IV d'antinéoplasique variait entre 12,34 $ et 64,19 $ la dose pour les 12 scénarios évalués (annexes 3 et 4).

Profil de l'établissement de santé universitaire type

Chaque établissement utilisait en moyenne, 32 767±11 234 fioles d'antinéoplasiques par année. La majorité des fioles, soit 80,9 % (26 509/32 767), avaient un diamètre de 20 mm et les autres, 19,1 %, avaient un diamètre de 13 mm (6 256/32 767). La majorité des doses IV, soit 81,6 %, étaient administrées en sacs (26 742/32 767), alors que l'administration des autres, soit 18,4 %, l'était en seringues (6 024/32 767). Les scénarios 11 et 12 représentaient la majorité des doses utilisées dans un établissement de santé universitaire type (47,8 %) (tableau 2). Nous avons regroupé les scénarios qui incluent un rinçage rétrograde et par seringue.

Estimation du coût annuel

L'estimation du coût annuel des fournitures du système classique pour la préparation et l'administration des doses IV d'antinéoplasiques dans un établissement de santé universitaire type se montait à 574 778 $. L'estimation du coût annuel des fournitures du système intégrant des SCTM pour la préparation et l'administration des doses IV d'antinéoplasiques dans un établissement de santé universitaire type variait entre 938 346 $ et 1 812 861 $ (Figure 1).

Tableau 2. Répartition du nombre de fioles par scénario retenu

	Scénario								
Paramètre	**1**	**2**	**3**	**4**	**5 et 6***	**7 et 8***	**9 et 10***	**11 et 12***	**Total**
Nombre moyen de fioles par établissement par année	1314	1496	853	2361	1552	6973	2538	15679	32767
Écart-type	578	721	508	1694	808	3311	1373	5429	11234
Proportion (%)	4	4,6	2,6	7,2	4,7	21,3	7,8	47,8	100

*Les scénarios ont été regroupés, car les numéros impairs correspondent à un rinçage avec une seringue et les numéros pairs correspondent à un rinçage rétrograde. Cela n'influence pas les proportions de fioles préparées en seringues ou en sacs dans l'établissement universitaire type.

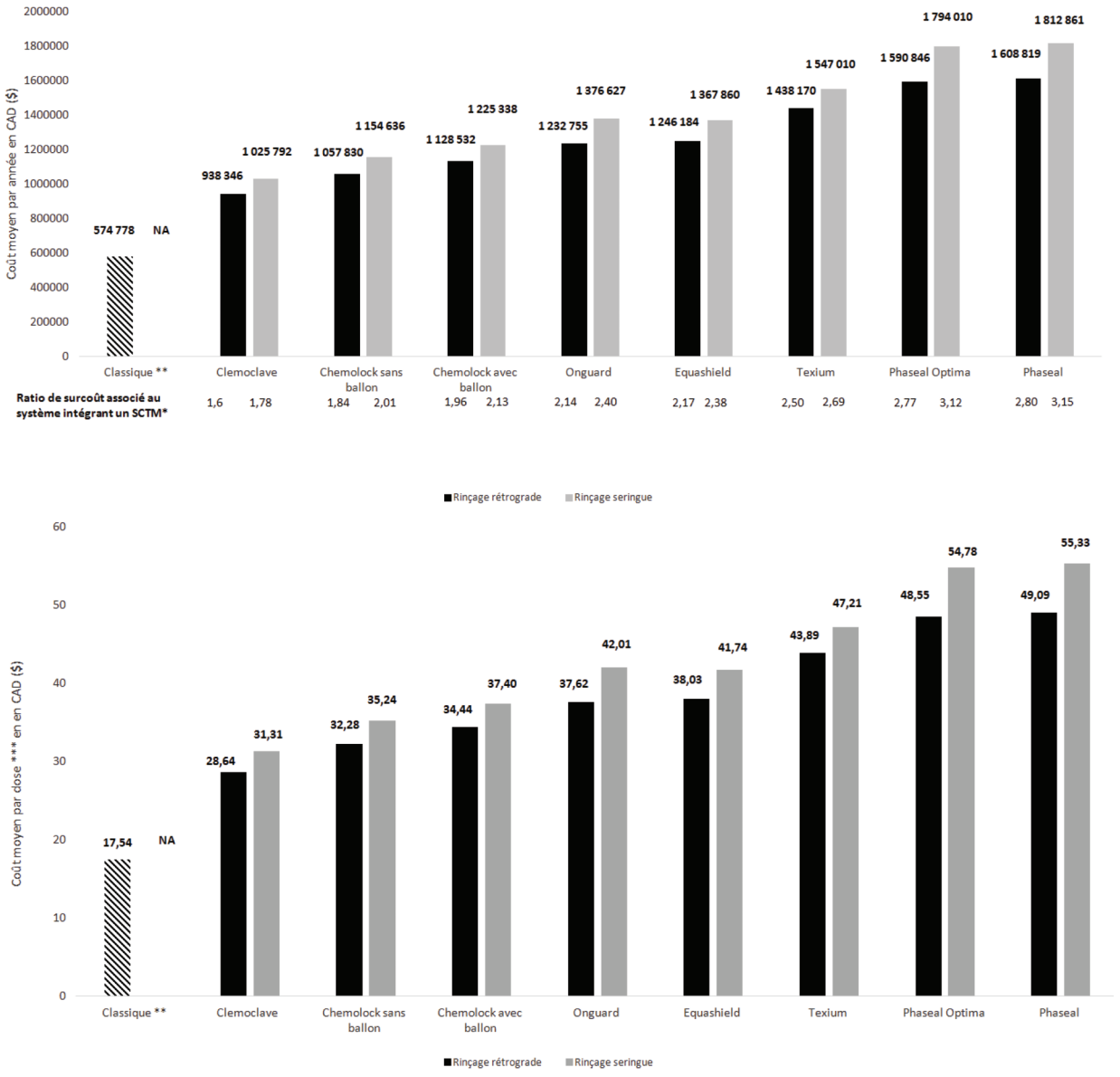

Figure 1. Coûts moyens par année et par dose ainsi que le surcoût associé à un système intégrant un système "clos de transfert de médicament (SCTM) pour un établissement de santé type. *Le surcoût des systèmes intégrant un SCTM par rapport au système classique a été calculé en divisant le coût annuel estimé du système intégrant un SCTM en particulier par le coût annuel estimé du système classique applicable. Puisque le rinçage avec la seringue est jugé non sécuritaire pour le système classique, tous les surcoûts ont été calculés en divisant par le coût annuel estimé du système classique avec rinçage rétrograde. **Pour le système classique, le rinçage à l'aiguille est jugé non sécuritaire. Noté NA (non applicable). ***Le coût moyen par dose a été calculé en divisant le coût moyen par année par le nombre moyen de dose par année.

Incinération des fournitures utilisées

En date du 1er septembre 2018, le coût d'incinération des déchets des antinéoplasiques était de 1,07 $/kg selon l'entente en vigueur à Sigmasanté. Pour un établissement universitaire type, le poids annuel des fournitures du système classique était de 4 190 kg, ce qui représente un coût moyen annuel d'incinération de 4 483,30 $. De plus, le poids annuel des fournitures des systèmes intégrant un SCTM (comprenant des fournitures classiques applicables) variait entre 4 655 et 5 622 kg, ce qui représente un coût moyen annuel d'incinération situé entre 4 980,85 $ et 6 015,54 $.

Incertitude

Les trois scénarios les plus représentatifs de la pratique dans un établissement de santé universitaire type ont servi à réaliser l'analyse d'incertitude, soit l'administration en seringues (scénario 4) et en sacs (scénarios 11 et 12). Le coût des fournitures nécessaires à la préparation et à l'administration d'une, de deux ou de trois doses d'antinéoplasiques par système pour les trois scénarios ciblés varie entre 3,49 $ et 17,44 $ par dose pour le système classique et entre 6,32 $ et 60,69 $ par dose pour un système intégrant un SCTM (tableau 3).

DISCUSSION

À notre connaissance, il s'agit de la première analyse de minimisation des coûts de préparation et d'administration

Tableau 3. Analyse d'incertitude – Coût par dose de la préparation et de l'administration d'une, de deux ou de trois doses par système pour trois scénarios ciblés

Système et variables	Préparation et administration d'une dose par système			Préparation et administration de deux doses par système			Préparation et administration de trois doses par système		
	Scénario 4	Scénario 11	Scénario12	Scénario 4	Scénario11	Scénario12	Scénario 4	Scénario11	Scénario12
Classique									
Nombre d'objets requis*	4	7	NA‡	2	4	NA‡	2	4	NA‡
Coût par dose†	9,89	17,44	NA‡	5,09	9,38	NA‡	3,49	6.68	NA‡
Chemoclave									
Nombre d'objets requis*	5§	11	13	3§	6	8	3§	6	8
Coût par dose†	12,34	30,82	34.09	7,82	20,08	23,35	6,32	16,50	19,77
Chemolock sans ballon									
Nombre d'objets requis*	6	12	14	3	6	8	3	6	8
Coût par dose†	15,14	34,47	38,09	9,40	22,68	26,30	7,48	18,75	22,37
Onguard									
Nombre d'objets requis*	5	11	13	2	5	7	2	5	7
Coût par dose†	18,24	40,50	45,88	11,70	27,52	32,90	9,52	23,20	28,58
Chemolock avec ballon									
Nombre d'objets requis*	6	12	14	3	6	8	3	6	8
Coût par dose†	18,59	37,92	41,54	11,12	24,41	28,03	8,63	19,90	23,52
Equashield									
Nombre d'objets requis*	6	12	14	3	6	8	3	6	8
Coût par dose†	19,67	40,68	45,23	12,73	27,26	31,81	10,41	22,79	27,34
Texium									
Nombre d'objets requis*	4	9	11	2	5	7	2	5	7
Coût par dose†	26,75	44,79	48,86	15,30	28,20	32,27	11,49	22,67	26,74
Phaseal Optima									
Nombre d'objets requis*	5	11	13	2	5	7	2	5	7
Coût par dose†	24,35	52,50	60,13	15,88	36,01	43,64	13,06	30,51	38,13
Phaseal									
Nombre d'objets requis*	6	12	14	3	6	8	3	6	8
Coût par dose†	24,91	53,06	60,69	16,41	36,54	44,17	13,58	31,03	38,66

NA = non applicable, coût par dose est en $ CA.
*Le nombre d'objets requis pour deux ou trois doses correspond aux fournitures nécessaires et non réutilisables dès la première dose (p. ex. seringue).
†Le coût par dose pour la deuxième dose est obtenu en additionnant les coûts d'acquisition des fournitures nécessaires (réutilisables et comptées une seule fois ainsi que non réutilisables et comptées deux fois) divisés par deux pour ramener à un coût par dose. Le même principe est appliqué pour la troisième dose.
‡Le rinçage par la seringue avec une aiguille est jugé non sécuritaire pour le système classique.
§Exemple du calcul du nombre d'objets pour le SCTM Chemoclave selon le scénario 4 (Fiole de 20 mm en solution, préparée pour une administration en seringue) : Dose 1, utilisation de 5 objets — Un adaptateur de fiole SCTM (réutilisation pour les autres doses), une seringue classique (non-réutilisation pour les autres doses), un adaptateur de seringue SCTM (non réutilisable pour les autres doses), un bouchon SCTM à mettre sur la seringue pour le transport dans le service (non réutilisable pour les autres doses), une tubulure d'administration classique reliée au patient, permettant de passer la seringue (réutilisation pour une autre dose au même patient). Pour cet exemple, on n'a pas besoin d'adaptateur SCTM raccordé à l'embout de la tubulure où sera placée la seringue, car la technologie du SCTM Chemoclave s'adapte à toutes les connexions Luer Lock. Ce n'est pas le cas de tous les SCTM (p. ex. Phaseal et Phaseal optima, Equashield, Onguard, Chemolock). Dose 2, utilisation de 3 objets — une seringue classique, un adaptateur de seringue, un bouchon à mettre sur la seringue. Dose 3, utilisation de 3 objets — une seringue classique, un adaptateur de seringue, un bouchon à mettre sur la seringue.

d'antinéoplasiques qui compare des systèmes intégrant les SCTM au Canada. L'estimation du coût annuel des fournitures pour la préparation et l'administration des doses d'antinéoplasiques dans un établissement de santé universitaire type induit par le système intégrant des SCTM variait entre 938 346 $ et 1 812 861 $, ce qui représente un coût moyen situé entre 28,64 $ et 55,32 $ par dose selon le SCTM. Le surcoût moyen annuel des systèmes intégrant un SCTM par rapport au système classique variait entre 1,63 fois et 3,15 fois, soit respectivement une dépense supplémentaire minimale de 363 568 $ par année et maximale de 1 238 083 $ par année. Les coûts liés aux fournitures requises pour la préparation et l'administration d'une dose IV d'antinéoplasique varient grandement. Le coût annuel moyen d'incinération des fournitures représente des frais négligeables par rapport aux coûts d'acquisition des fournitures. Si on tient compte en outre de la possibilité de préparer ou d'administrer deux ou trois doses d'antinéoplasiques avec les mêmes fournitures, les coûts peuvent varier énormément. La réutilisation des fournitures, quand cela est possible, permet de diminuer les coûts à la fois dans le groupe des systèmes classiques et dans celui des SCTM.

Une revue de la littérature publiée récemment recense seulement 12 articles présentant les coûts associés à un système intégrant un SCTM[21]. Ces publications étaient souvent incomplètes (moyenne de 9,2/24 critères CHEERS rapportés). Les coûts rapportés dans la littérature concernaient majoritairement le système Phaseal. Nous avons cependant répertorié sur le marché canadien sept SCTM possibles. Les coûts retrouvés dans les études sont hétérogènes et difficilement comparables (c.-à-d. devises différentes, barème de calcul des coûts variable, qui inclut le coût annuel, le coût par dose, le coût pour la préparation seulement, etc.). Mullot et collab. rapportaient une estimation des coûts annuels de 160 000 € liés au système Phaseal pour la préparation d'environ 24 400 doses d'antinéoplasiques[26]. Edwards et collab. rapportaient des coûts annuels de 106 557 $ US pour la pharmacie ayant recours au SCTM de type Phaseal[27]. Ces estimations de coûts sont inférieures à nos calculs, mais elles ne prennent pas en compte les coûts liés à l'administration des doses. Une autre étude évaluant les coûts d'acquisition liés à un système intégrant le Phaseal pour la préparation rapporte des frais de 40,92 $ US par dose[28]. Ce coût par dose se rapproche davantage des 55,32 $ par dose de notre analyse, qui représentent le coût moyen par dose d'un système intégrant Phaseal. Par ailleurs, un hôpital nord-américain a estimé le coût annuel d'implantation d'un SCTM à 1,5 millions $ US, ce qui se rapproche davantage des intervalles calculés dans notre étude[22].

Selon le chapitre 797 de l'United States Pharmacopeia (USP), les fioles à dose unique utilisées pour les préparations stériles effectuées dans des conditions ISO5 doivent comporter une date limite d'utilisation (DLU) de six heures pour limiter le risque de contamination microbienne[29]. L'Association nationale des organismes de réglementation de la pharmacie (ANORP) recommande également une DLU de six heures[10]. L'Ordre des pharmaciens du Québec (OPQ) recommande une DLU de 24 h[11]. Quelques auteurs ont observé que les coûts d'acquisition associés aux systèmes intégrant un SCTM pourraient être compensés par une économie associée à la prolongation de la DLU envisagée lorsqu'on utilise un système intégrant un SCTM[27,30,31]. Peu d'études ont comparé la stérilité des fioles percées à l'aide d'un sytème classique et de systèmes intégrant un SCTM[32-34]. Une revue de littérature sur le sujet confirme cette lacune[35]. De plus, aucun organisme n'appuie actuellement la prolongation de la DLU avec l'utilisation de systèmes intégrant un SCTM[6,11,29]. En outre, une méta-analyse récente montre un faible taux de contamination (0,08 %) des fioles préparées à la pharmacie (intervalle de confiance à 95 % 0-0) et cela sans mention d'utilisation de SCTM[36]. Chaque établissement de santé devrait évaluer son risque de base. Il n'est peut-être pas possible de démontrer la réduction accrue de la contamination en utilisant un système intégrant un SCTM, compte tenu du très faible taux de contamination de base. La décision de prolonger la DLU devrait être discutée avec l'organisme réglementaire concerné.

Différentes mesures contribuent à limiter les risques liés à l'exposition professionnelle des travailleurs aux antinéoplasiques (p. ex. nettoyer les fioles contaminées à leur réception à la pharmacie, porter des équipements de protection individuelle, respecter les bonnes pratiques de préparation)[1,7,37]. Les SCTM font partie de ces mesures. Les professionnels de la santé et particulièrement ceux qui exercent au chevet des patients sont exposés à des traces de médicaments dangereux lors de l'administration d'une dose d'antinéoplasique. Toutefois, l'exposition aux excreta des patients est une source de contamination non négligeable qui ne peut pas être réduite par les systèmes intégrant un SCTM. Dans la revue Cochrane portant sur l'efficacité des systèmes intégrant un SCTM, les auteurs ont noté une faible réduction des traces de cyclophosphamide (50 pg/cm^2) et d'épirubicine (110 pg/cm^2) à la pharmacie, mais pas pour les autres antinéoplasiques étudiés, en dépit de l'utilisation de systèmes intégrant un SCTM. Cette revue systématique ne permet pas non plus de confirmer la provenance des traces (c.-à-d. contenant de médicament, tubulure, excreta)[20]. Ainsi, compte tenu des coûts élevés associés à l'utilisation des SCTM, la décision de les utiliser doit s'appuyer sur le recours à toutes les autres mesures de protection des travailleurs et de réduction du risque. Il convient de préciser que les systèmes i ntégrant un SCTM sont une option permettant de retirer les aiguilles pour la préparation et l'administration des doses d'antinéoplasiques par voie parentérale.

Du fait des coûts élevés associés aux systèmes intégrant un SCTM, la sélection d'un SCTM en particulier devrait prendre en compte les données probantes, l'évaluation de la mise en place adéquate des autres mesures de protection des travailleurs, l'analyse actuelle des contaminations de surface de l'établissement, une

analyse économique comparative des pratiques actuelles et des systèmes envisagés intégrant un SCTM. Il semble également utile que la sélection d'un système intégrant un SCTM se fasse dans le cadre d'un appel d'offres régional ou national afin d'obtenir les meilleurs prix.

Dans le chapitre 800 de l'USP, les experts recommandent l'utilisation rigoureuse d'un système intégrant un SCTM pour l'administration de doses d'antinéoplasiques lorsque cela est possible (critère 5.4) tout en évoquant l'utilité d'un tel système pour la préparation, sans en exiger l'usage. Il est possible de réduire les coûts associés à l'utilisation de SCTM en ne retenant que les fournitures utilisées pour l'administration des doses (c.-à-d. adaptateur permettant à l'infirmière de raccorder de façon étanche une seringue ou un sac aux tubulures utilisées pour l'administration) et en excluant les fournitures spécifiques à la préparation (p. ex. adaptateur de fiole). Notre analyse ne comporte pas de tels scénarios.

Cette analyse de minimisation de coûts ne cible que les fournitures utilisées pour la préparation et l'administration d'une dose IV d'antinéoplasique en date du 1er septembre 2018. Dans cette étude, une fiole correspond à une dose pour un patient, ce qui représente une analyse prudente, car une fiole peut être utilisée pour d'autres doses destinées à d'autres patients. Il est également possible que plusieurs fioles soient nécessaires pour un même patient. Une future analyse devrait prendre en compte le nombre de doses préparées par un établissement et non le nombre de fioles afin que l'analyse de la consommation soit plus fine. Pour les fins de cette analyse, nous avons interrogé trois établissements de santé qui sont représentatifs des établissements universitaires du Québec, mais qui ne reflètent pas à eux seuls les pratiques de la province. De plus, l'analyse ne tient pas compte des coûts liés aux infrastructures, à l'achat de médicaments, à l'utilisation d'autres fournitures, aux ressources humaines et de gestion. D'autres scénarios pourraient être envisagés, compte tenu des pratiques locales. L'analyse ne tient pas compte des avantages et des inconvénients associés à chaque système. Chaque fabricant de SCTM met en valeur les avantages de ses produits et il existe des différences entre les systèmes qui peuvent influencer les préférences des utilisateurs en termes d'ergonomie et de temps de manipulation. Compte tenu des différents concepts de SCTM, des données publiées et de l'absence d'un protocole valide permettant de comparer l'efficacité de chaque SCTM, nous avons choisi de prendre en considération les systèmes équivalents. D'autres travaux pourraient comparer les coûts associés aux manipulations des divers SCTM (c.-à-d. temps-mouvements).

CONCLUSION

Le système classique engendre des coûts de fournitures nécessaires à la préparation et à l'administration d'une dose d'antinéoplasique qui varient entre 9,89 $ et 22,37 $ la dose et les coûts des systèmes intégrant un SCTM se situent entre 12,34 $ et 64,19 $ la dose. Le surcoût moyen annuel des systèmes intégrant un SCTM par rapport au système classique est de 1,63 fois à 3,15 fois supérieur et il représente une dépense annuelle supplémentaire de 363 566 $ à 1 238 072 $ pour un établissement de santé universitaire type pour adultes. Compte tenu des coûts importants associés à la préparation et à l'administration des antinéoplasiques, les décideurs devraient mener des analyses complètes des coûts et des conséquences afin de prendre des décisions éclairées.

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Efficacy, Safety, and Practicality of Tacrolimus Monitoring after Bone Marrow Transplant: Assessment of a Change in Practice

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ABSTRACT

Background: Currently, there is no standardized approach to the frequency of monitoring tacrolimus levels in patients who have undergone hematopoietic stem cell transplant (HSCT). Previously, the practice at the study hospital was to monitor tacrolimus levels daily throughout a patient's admission. A recent institutional study suggested that measurement of tacrolimus level is more frequent than needed to achieve consistent time in the therapeutic range (TTR), particularly after the first 7 days. As a result, tacrolimus monitoring was changed to daily measurement for the initial week of therapy, followed by measurements on Monday, Wednesday, and Friday in subsequent weeks.

Objective: To confirm the safety and efficacy of the recent practice change.

Methods: This retrospective chart review of HSCT patients admitted to The Ottawa Hospital involved 68 patients in the pre–practice change group and 43 patients in the post–practice change group. Data on tacrolimus measurement were collected for up to 21 days after initiation of this medication. The proportion of TTR was compared between the 2 groups. Differences in the incidence and severity of renal dysfunction and the incidence of acute graft versus host disease (GVHD) were determined and described.

Results: In the pre–practice change cohort, the median proportion of TTR for tacrolimus was 40.5% for days 1–7, 65.1% for days 8–14, and 78.9% for days 15–21, similar to the values for the post–practice change group (46.6% [p = 0.09], 62.9% [p = 0.93], and 70.0% [p = 0.22], respectively, for the same periods). The incidence of acute GVHD within 100 days after HSCT was 24% and 33% for the pre– and post–practice change cohorts, respectively. The incidence and severity of renal dysfunction were similar between the 2 groups.

Conclusion: The proportion of TTR for tacrolimus was not significantly affected by the recent practice change. Similarly, the incidence and severity of renal dysfunction and the incidence of acute GVHD did not appear to differ between the pre– and post–practice change groups.

Keywords: tacrolimus, acute graft-versus-host disease, time in therapeutic range, renal dysfunction, monitoring

RÉSUMÉ

Contexte : Il n'existe actuellement aucune approche standardisée portant sur la fréquence des contrôles des valeurs du tacrolimus pour les patients ayant subi une greffe de cellules souches hématopoïétiques (GCSH). Dans le passé, la pratique à l'hôpital où s'est déroulée l'étude consistait à les contrôler quotidiennement durant tout le séjour du patient. Une récente étude institutionnelle a laissé entendre que cette mesure était plus fréquente que nécessaire pour obtenir une marge thérapeutique régulière (TTR), particulièrement après les sept premiers jours. Par conséquent, une modification du contrôle des valeurs du tacrolimus préconise désormais des mesures quotidiennes pendant la première semaine de la thérapie, suivies de mesures le lundi, le mercredi et le vendredi au cours des semaines suivantes.

Objectif : Confirmer la sécurité et l'efficacité du récent changement apporté à la pratique.

Méthode : Cet examen rétrospectif des dossiers des patients GCSH admis à l'Hôpital d'Ottawa concernait 68 patients du groupe « avant le changement de pratique » et 43 du groupe « après le changement de pratique ». Les données relatives aux mesures des valeurs du tacrolimus ont été recueillies pendant les 21 premiers jours après le début de l'administration de ce médicament. La comparaison entre les deux groupes portait sur la proportion de TTR. Les différences d'incidence et de gravité du dysfonctionnement rénal et l'apparition de réaction aiguë du greffon contre l'hôte (GVHD) ont été définies et décrites.

Résultats : Dans la cohorte « avant le changement de pratique », la proportion moyenne de TTR du tacrolimus était de 40,5 % du 1er au 7e jour; de 65,1 % du 8e au 14e jour et de 78,9 % du 15e au 21e jour. Ces valeurs sont similaires à celles du groupe « après le changement de pratique » (respectivement 46,6 % [p = 0,09], 62,9 % [p = 0,93] et 70,0 % [p = 0,22] pendant les mêmes périodes). L'incidence de réaction aiguë du greffon contre l'hôte dans les 100 jours après la GCSH se montait respectivement à 24 % et à 33 % dans les cohortes « avant et après le changement de pratique ». L'incidence et la gravité du dysfonctionnement rénal étaient similaires dans les deux groupes.

Conclusion : La proportion de TTR relative au tacrolimus n'a pas été modifiée de manière significative par le changement récent de pratique. De même, l'incidence et la gravité du dysfonctionnement rénal et l'incidence de réaction aiguë du greffon contre l'hôte ne semblaient pas différer entre les groupes avant et après le changement de pratique.

Mots-clés : tacrolimus, réaction aiguë du greffon contre l'hôte, marge thérapeutique, dysfonctionnement rénal, contrôle

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INTRODUCTION

For various hematological malignancies, allogeneic bone marrow transplant (also known as hematopoietic stem cell transplant [HSCT]) is a potentially curative treatment in which hematopoietic cells are retrieved from human leukocyte antigen–matched donors.[1] Upon completion of a chemotherapy conditioning regimen, patients receive an infusion of matched cells.[2] A potentially fatal complication of HSCT is graft-versus-host disease (GVHD), in which donor-derived immune cells, primarily T lymphocytes, trigger an immunological response against the recipient's tissues.[3] The organs most often affected by GVHD are the skin, gastrointestinal tract, and liver.[4] Although the success of HSCT has improved, 35% to 50% of post-transplant patients still experience GVHD, which illustrates the importance of GVHD prophylaxis after allogeneic HSCT to prevent further morbidity or mortality.[5]

Acute GVHD is the second leading cause of mortality among patients who have undergone allogeneic HSCT.[6] Historically, GVHD that manifested within 100 days after HSCT was defined as acute, and GVHD that manifested 100 days or more after the transplant was termed chronic.[7] Classic acute GVHD has a characteristic presentation of erythema, maculopapular rash, nausea, vomiting, profuse diarrhea, ileus, or cholestatic liver disease.[8]

Tacrolimus is an immunosuppressant that has proven effective in preventing GVHD when used in combination with methotrexate.[9] Tacrolimus inhibits T-lymphocyte activation by forming a complex with FK-binding protein 12, which blocks the serine-threonine phosphatase activity of calcineurin.[9,10] This blockage in the serine-threonine phosphatase activity of calcineurin results in inhibition of the further downstream signal transduction that occurs with GVHD.[10]

It has been reported that about 25% to 50% of all patients undergoing bone marrow transplant experience acute kidney injury.[11] GVHD, hepatic veno-occlusive disease, and high-dose radiation with fluid loss due to diarrhea and vomiting can cause renal failure. An adverse effect of tacrolimus is renal dysfunction, and this adverse effect may be caused by other drugs as well.[11] The nephrotoxicity of calcineurin inhibitors, such as tacrolimus, is due to vasoconstriction of the afferent renal arterioles. More than half of patients who are taking tacrolimus will experience a doubling of their baseline serum creatinine.[12] It appears that calcineurin inhibitors influence renal function in a dose-dependent manner.[11] Management of acute kidney injury mainly involves supportive care, such as withdrawal of nephrotoxic drugs and dose reduction of calcineurin inhibitors.[13]

The standard of kinetic tacrolimus monitoring is the measurement of trough concentrations.[14] The target trough level of tacrolimus, as reported in the literature, ranges from 5 to 20 µg/L.[14-16] Tacrolimus levels below 5 µg/L have increased the risk of GVHD, whereas levels above 20 µg/L have been associated with nephrotoxicity.[15] Although the monitoring of tacrolimus levels in the blood is important to prevent complications, the optimal frequency of monitoring in patients who have undergone HSCT is currently unknown, because there is no standard guideline or recommendation for tacrolimus in the setting of HSCT. Furthermore, no target proportion of time in therapeutic range (TTR) has been reported in the literature. This lack of evidence is apparent from the lack of a standardized process for tacrolimus monitoring in HSCT patients across Canadian transplant centres (Table 1). Initial dosing of tacrolimus, route of administration, target levels, and frequency of monitoring all vary among institutions.

Table 1. Use of Tacrolimus at Other Canadian Institutions

Institute (Location)	Tacrolimus Dosage	Target Level	Frequency of Monitoring	Clinician Responsible for Monitoring
Princess Margaret Hospital (Toronto, Ontario)	0.015 mg/kg IV q12h	7–15 µg/L	Twice weekly	Pharmacist, physician
Hamilton Health Sciences (Hamilton, Ontario)	1 mg over 24 h by continuous IV infusion	5–15 µg/L	Daily for 4 or 5 days, then 3 times weekly	Pharmacist, physician, nurse practitioner (outpatient setting)
Cancer Care Manitoba (Winnipeg, Manitoba)	0.03 mg/kg over 24 h by continuous IV infusion (myeloablative), 0.2 mg/kg per day PO divided q12h	8–12 µg/L initially, then 5–15 µg/L at day 50 post-transplant and beyond	Twice weekly for inpatients, once weekly for outpatients	Pharmacist, physician
Baker Cancer Centre (Calgary, Alberta)	0.12–0.15 mg/kg per day PO divided q12h or 0.03 mg/kg over 24 h by continuous IV infusion	5–15 µg/L	Three times weekly for inpatients, once weekly for outpatients	Pharmacist
Nova Scotia Health Authority (Halifax, Nova Scotia)	3 mg PO bid (non-myeloablative transplant)	5–15 µg/L	Twice weekly	Pharmacist, physician, nurse practitioner (outpatient)
Eastern Health (St John's, Newfoundland)	3 mg PO bid	5–15 µg/L	Twice weekly	Nurse practitioner (outpatient)
Vancouver Coastal Health (Vancouver, British Columbia)	0.03 mg/kg over 24 h by continuous IV infusion	5–10 µg/L	Twice weekly	Pharmacist

At The Ottawa Hospital, tacrolimus is used in combination with methotrexate for GVHD prophylaxis in patients undergoing HSCT. Tacrolimus is usually initiated 3 days before the transplant procedure (i.e., day –3). The immediate-release formulation of tacrolimus (Prograf) is given to all patients orally at a dose of 0.13 mg/kg per day, divided every 12 h and adjusted to maintain the target trough level between 5 and 10 µg/L.

This study was based on a previous (unpublished) retrospective pilot study performed in 2016, when samples for measurement of tacrolimus levels were drawn daily at the study institution. That pilot study showed that dosing interventions were made frequently during the first 7 days of tacrolimus therapy, when levels are monitored daily. After the first 7 tacrolimus measurements, TTR and number of dosing interventions remained steady between the 8th and 14th measurements and between the 15th and 21st measurements, across a range of patient characteristics. That pilot study also described the initial dosing of tacrolimus, compared the proportion of TTR between the three 7-day intervals (over the total course of 21 measurements), and compared the proportion of TTR between different groups of patients (those who had inpatient versus outpatient procedures; those receiving versus not receiving interacting medications). It was shown that monitoring tacrolimus levels daily after day 7 of tacrolimus therapy did not significantly affect the proportion of TTR. Over the first 7 measurements, the mean proportion of TTR was 46%; TTR increased to 64% over measurements 8 to 14 and increased further to 67% over measurements 15 to 21. For all patients in the pilot study, tacrolimus level was measured daily for at least the first 14 days of therapy, after which, on the basis of clinician judgment and preference, monitoring frequency was reduced to 3 times weekly (Monday, Wednesday, and Friday) for 45% of patients; the remaining 55% of patients continued to undergo daily monitoring. Although the frequency of monitoring changed, the proportion of TTR stayed consistent. This observation was hypothesis-generating and suggested that, at this institution, tacrolimus levels were measured more frequently than needed to achieve consistent TTR during inpatient care, particularly after the first 7 days. The pilot study found no difference in TTR for patients using interacting drugs, such as proton pump inhibitors and azole antifungals, which confirmed the practitioners' existing practice to empirically reduce tacrolimus dosage in conjunction with interacting medications. There was also no difference in tacrolimus TTR according to whether patients received their transplant as an inpatient or an outpatient.

The results of that pilot study led to a change, in August 2017, in tacrolimus monitoring practice within the Blood and Marrow Transplant program at The Ottawa Hospital. Previously, according to institutional recommendations, tacrolimus levels were measured daily for an indeterminate period during the hospital admission. The practice change involved drawing samples for measurement of tacrolimus levels daily for the first week of tacrolimus therapy and then on Monday, Wednesday, and Friday each week until hospital discharge or cessation of therapy. The current study was conducted to validate the recent practice change in tacrolimus monitoring and to ensure that measures of TTR, safety, and practicality were comparable between the pre– and post–practice change groups of patients.

The objectives of this retrospective study were as follows:

- to compare the median proportion of TTR for tacrolimus between a pre–practice change group and a post–practice change group of HSCT patients
- to describe the incidence of acute GVHD within 100 days after transplant in the pre–practice change group and the post–practice change group of HSCT patients receiving tacrolimus therapy
- to describe the incidence and severity of renal failure within 30 days after initiating tacrolimus therapy in the pre–practice change group and the post–practice change group of HSCT patients receiving tacrolimus therapy
- to describe the total number of samples drawn for tacrolimus measurement overall and per weekend day in the pre–practice change group and the post–practice change group of HSCT patients receiving tacrolimus therapy
- to describe the number of protocol deviations that occurred during the study period

METHODS

A retrospective chart review was conducted to assess the change in standard of practice at The Ottawa Hospital. The pre–practice change group consisted of patients who underwent HSCT at this hospital between November 1, 2015, and October 31, 2016. The post–practice change comparator group consisted of patients who underwent HSCT at the same hospital between September 1, 2017, and February 28, 2018. The difference in study duration between the 2 groups was related to use of a convenience sample and the time constraints of a pharmacy residency year. Patients had to have received GVHD prophylaxis with oral tacrolimus for at least 21 days to be eligible for inclusion in the study. Those who had received their transplant at an institution other than The Ottawa Hospital were excluded.

Patients who had received oral tacrolimus for at least 21 days during the periods of interest were identified from pharmacy records. The patient list generated in this way was screened against the inclusion criteria described above to determine eligibility.

Data for serum tacrolimus levels were collected from electronic health records at The Ottawa Hospital. For each patient, the first level reported after the day of initiation of tacrolimus was collected. The day of initiation of tacrolimus therapy was defined relative to the day of transplant, with the day of transplant being denoted as "day 0". All tacrolimus levels reported between the day of initiation to 21 days after initiation were recorded.

The proportion of TTR was defined as the proportion of time that a patient's tacrolimus levels were within the institutionally accepted therapeutic range of 5 to 10 µg/L, relative to the total period studied for that patient. The proportion of TTR between 2 consecutive levels was extrapolated using a pharmacokinetic geometric model, with thresholds of 5 and 10 µg/L.

The incidence of acute GVHD was assessed using the surrogate marker of systemic steroid initiation, corroborated by clinical notes describing suspected acute GVHD, as documented at the time of patient care.

Data for serum creatinine levels were collected for 30 days after initiation of tacrolimus therapy. The incidence and severity of renal dysfunction were assessed with the Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury staging criteria (Table 2) and a comparison between baseline and peak serum creatinine levels. The serum creatinine level recorded on day 1 was considered as the baseline.

Protocol deviations were defined, within the post–practice change group, as measurements based on samples that were drawn on days other than Monday, Wednesday, or Friday, or measurements that were missed on those days during the study period.

An in-service education session was provided to nursing staff at the end of November 2017 (about 3 months after the change in monitoring frequency) to reinforce uptake of the practice change.

To compare the proportion of TTR between the 2 groups, a Mann-Whitney *U* test was performed with SPSS software (version 20, IBM Corporation, Armonk, New York). For the other 4 research objectives, data were analyzed using descriptive statistics.

Table 2. Staging of Acute Kidney Injury*

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 mmol/l) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

eGFR = estimated glomerular filtration rate.
*Reproduced, with permission, from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1-138.

Table 3. Patient Characteristics

Characteristic	Timing; No. (%) of Patients*	
	Before Practice Change (*n* = 68)	After Practice Change (*n* = 43)
Age (years) (mean and range)	50 (18-70)	51 (18-73)
Age ≥ 65 years	5 (7)	10 (23)
Sex, male	43 (63)	28 (65)
Serum creatinine (µmol/L) (mean and range)	61 (31–113)	62 (39–104)
Indication for HSCT		
Acute leukemia†	30 (44)	25 (58)
Chronic leukemia‡	6 (9)	5 (12)
Myelodysplastic syndrome	10 (15)	6 (14)
Non-Hodgkin lymphoma	11 (16)	4 (9)
Aplastic anemia	5 (7)	0 (0)
Multiple myeloma	4 (6)	0 (0)
Myelofibrosis	2 (3)	2 (5)
Krabbe disease	0 (0)	1 (2)

HSCT = hematopoietic stem cell transplant.
*Except where indicated otherwise.
†Acute myeloid leukemia, acute lymphoblastic leukemia.
‡Chronic myelogenous leukemia, chronic myelomonocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, prolymphocytic leukemia.

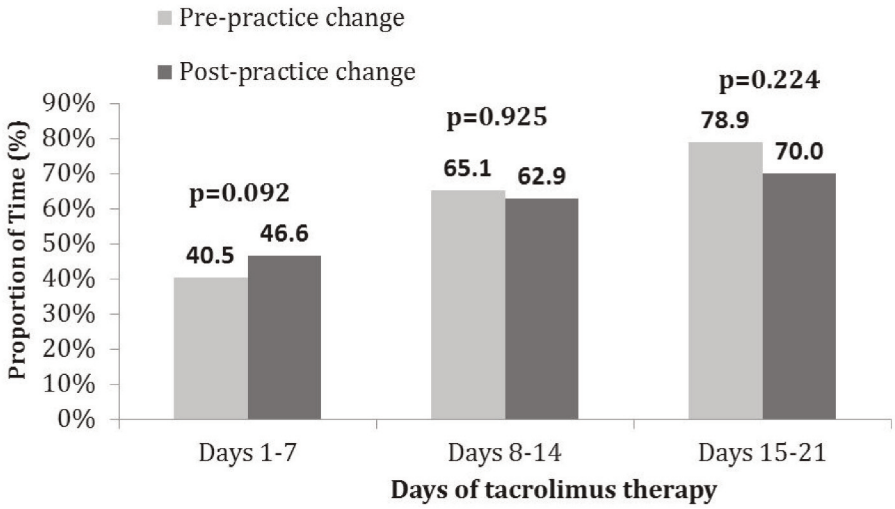

Figure 1. Median proportion of time with tacrolimus within therapeutic range.

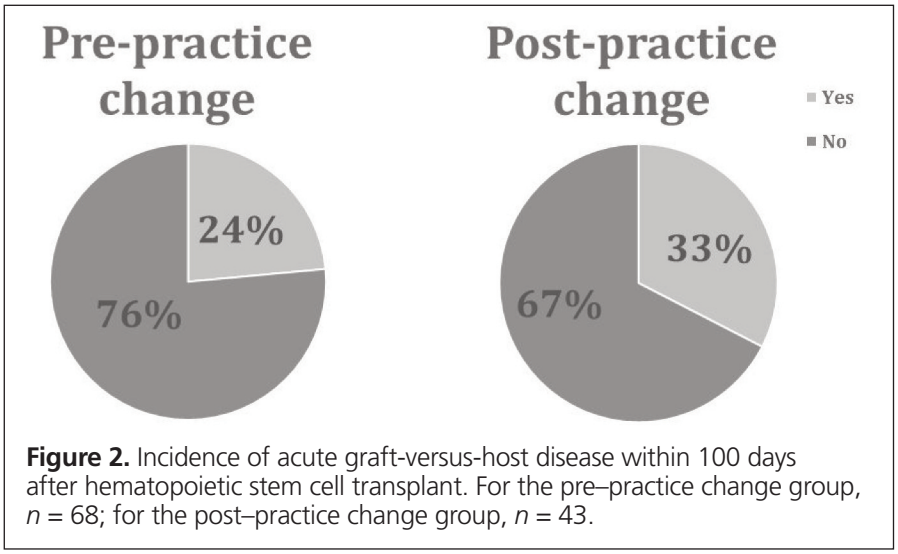

Figure 2. Incidence of acute graft-versus-host disease within 100 days after hematopoietic stem cell transplant. For the pre–practice change group, $n = 68$; for the post–practice change group, $n = 43$.

RESULTS

The pre–practice change group had a total of 68 patients, and the post–practice change group had a total of 43 patients. The mean age, proportions of men and women, and baseline serum creatinine were similar between the 2 groups (Table 3), but the proportion of patients older than 65 years was higher in the post–practice change group. The indications for HSCT were similar between the 2 groups. The initial dose of tacrolimus varied among patients because the starting dose for this drug is weight-based.

The median proportion of TTR did not differ between groups in the first 7 days of tacrolimus therapy: 40.5% in the pre–practice change group and 46.6% in the post–practice change group ($p = 0.09$) (Figure 1). Similarly, there was no difference between the groups in median proportion of TTR for days 8–14 (65.1% versus 62.9%, $p = 0.93$) and days 15–21 (78.9% versus 70.0%, $p = 0.22$).

The incidence of acute GVHD within 100 days after HSCT was 24% (16/68) in the pre–practice change group and 33% (14/43) in the post–practice change group (Figure 2).

The incidence of all-stage renal dysfunction within 30 days after HSCT was 65% in the pre–practice change group and 70% in the post–practice change group (Table 4). In the pre–practice change group, 38% of patients had stage 1 renal dysfunction, 16% had stage 2 renal dysfunction, and 10% had stage 3 renal dysfunction. In the post–practice change group, 42%, 16%, and 12% of patients had stage 1, stage 2, and stage 3 renal dysfunction, respectively.

In total, 1280 and 584 samples were drawn for measurement of tacrolimus during the study period for the pre–and post–practice change groups, respectively, for an average of 19 and

14 samples per patient, respectively (Table 5). Of these samples, 347 and 100 were drawn on weekends for the pre–and post–practice change groups, for an average of 0.85 and 0.39 samples per weekend day, respectively (Table 5).

Overall, there were a total of 99 protocol deviations after the practice change, for an average of 2.3 deviations per patient (Table 6). Of these 99 protocol deviations, 65 occurred before and 34 after delivery of the in-service nursing education session (Table 6), for an average of 3.1 protocol deviations per patient before and 1.5 protocol deviations per patient after the nursing education session (Table 6). Protocol deviations included both missed measurements (i.e., missed on Monday, Wednesday, or Friday or at any point during the first 7 days of therapy) and extra measurements (i.e., on a day other than Monday, Wednesday, or Friday).

DISCUSSION

This study aimed to assess efficacy and safety outcomes, including proportion of TTR for tacrolimus, incidence of acute GVHD, and incidence and severity of renal dysfunction in patients who have undergone allogeneic HSCT, after a change in the standard of practice for tacrolimus monitoring at the study institution. There is currently a lack of evidence about optimal monitoring frequency of tacrolimus levels, and there is no standardized approach across all Canadian transplant centres. To our knowledge, this is the first study comparing different frequencies of tacrolimus monitoring in the setting of allogeneic HSCT.

In this study, we used proportion of TTR as a marker to assess how well tacrolimus levels were maintained during therapy. Use of proportion of TTR as a marker for tacrolimus effectiveness has been employed in other studies.[17,18] Because the data for this variable did not show a normal distribution, we reported median values. Although there were small differences in the proportion of TTR between the 2 study groups, they were not statistically or clinically significant. The results suggest that switching the monitoring frequency of tacrolimus from once daily for the entire hospital stay to once daily for the first 7 days of therapy and then 3 times weekly did not affect the overall proportion of TTR. In addition, some centres monitor tacrolimus less frequently than daily for the first 7 days (Table 1).

In 2 previous studies, the blood levels of tacrolimus significantly affected development of grades II to IV acute GVHD.[19,20] However, those studies also found differing ranges of tacrolimus blood levels between patients with grade 0 or I acute GVHD

Table 4. Incidence of Renal Dysfunction with 30 days after Hematopoietic Stem Cell Transplant

Stage of Renal Dysfunction	Timing; No. of Patients	
	Before Practice Change (*n* = 68)	After Practice Change (*n* = 43)
All stages	44 (65)	30 (70)
1	26 (38)	18 (42)
2	11 (16)	7 (16)
3	7 (10)	5 (12)

Table 5. Samples Drawn for Measurement of Tacrolimus Level

Variable	Before Practice Change (*n* = 68)	After Practice Change (*n* = 43)
Total no. of samples drawn	1280	584
Mean no. of samples per patient	19	14
Total no. of samples drawn on weekends	347	100
No. of weekend days	408	258
No. of weekend samples per weekend day	0.85	0.39

Table 6. Protocol Deviations after Practice Change

Timeframe	Total No. of Deviations	Mean No. of Deviations per Patient
Overall study period (*n* = 43 patients)	99	2.3
Before nursing education (*n* = 21 patients)	65	3.1
After nursing education (*n* = 22 patients)	34	1.5

and those with grade II to IV acute GVHD (> 7 ng/mL and 10–20 ng/mL, respectively).[19,20] Gao and others[21] found that the incidence of acute GVHD in haploidentical HSCT patients, with tacrolimus levels between 10 and 15 µg/L, was 29.1%. Watanabe and others[19] reported a 34.8% incidence of acute GVHD in pediatric patients who had undergone allogeneic HSCT and were receiving tacrolimus, with tacrolimus levels of at least 7 µg/L. Nash and others[9] showed a 56% probability of acute GVHD based on a Kaplan-Meier estimate, which is higher than the incidence reported in the other studies mentioned. Overall, these incidence values for acute GVHD are consistent with our study results. Our study did not aim to statistically analyze the difference in incidence of acute GVHD because the study population was small. Continued monitoring for acute GVHD in the post–practice change group may be warranted for future studies.

With regard to kidney dysfunction, we found similar incidence and severity between the pre– and post–practice change groups, which suggests that the change in tacrolimus monitoring practice did not affect renal function. However, this study used only peak serum creatinine values to assess renal dysfunction. We did not consider urine output, which is also included in the KDIGO staging criteria,[22] because patients were being monitored as outpatients and urine output could not be tracked. This study described but did not analyze the difference in incidence and severity of renal dysfunction between the 2 study groups. Continued monitoring for renal dysfunction in the post–practice change group should be explored in future studies.

Partway through the study period, we delivered an in-service nursing education session to justify, promote, and remind staff in the Blood and Marrow Transplant program about the recent practice change at our institution, The intent of this education session was to prevent or reduce potential protocol deviations. Although protocol deviations occurred even after nursing education, they could be attributed to the fact that patients were sometimes given "days off" from follow-up if the physician deemed their condition to be stable. When patients missed a tacrolimus measurement on an intended day, a sample was sometimes drawn on another day, outside of the defined protocol.

Overall in this study, the average number of tacrolimus measurements per patient decreased from 19 before to 14 after implementation of the practice change. In practical terms, this resulted in fewer early morning follow-up visits for patients, fewer blood samples being sent to the laboratory for analysis, and a reduced workload for nurses and pharmacists. There was also a decrease in the number of measurements per weekend day, from 0.85 to 0.39, after the practice change. Fewer weekend measurements would help to improve weekend nursing and pharmacy workloads, at a time when fewer staff are scheduled. In addition, based on an average cost of $15 per tacrolimus measurement and an average of 100 HSCT patients per year at the study institution, the overall reduction in tacrolimus measurements would equate to about $7500 of direct savings per year.

This study had several limitations. The surrogate marker of systemic steroid initiation that was used to determine the incidence of acute GVHD would have excluded less severe cases treated only with topical corticosteroids and thus might have led to underestimation of the true incidence of acute GVHD. In addition, as stated previously, the small sample size limited our ability to compare differences in acute GVHD incidence. Because of the retrospective study design, the indications for transplant were not balanced between the groups, and patients with different indications would receive different conditioning regimens. However, this study realistically reflects the blood and marrow transplant practice setting. Another limitation was use of the surrogate marker of peak serum creatinine to determine renal dysfunction. Use of this marker might have overestimated the true incidence and severity of renal dysfunction, because factors such as dehydration and concomitant nephrotoxic therapy might have caused a transient spike in serum creatinine, and the patterns of serum creatinine change would not have been taken into account. Finally, the 2 study groups had differing sample sizes, because the time constraints for a pharmacy resident project dictated use of a convenience sample. More specifically, the inclusion period was shorter for the post–practice change group than for the pre–practice change group, which likely explains the lower number of patients during the post–practice change period. However, the results appeared consistent between the 2 groups, despite the lower denominator, and we do not believe the difference in the number of patients between the 2 groups would have significantly affected the results.

CONCLUSION

This study showed that monitoring tacrolimus levels daily for the first 7 days of therapy and then each Monday, Wednesday, and Friday thereafter did not result in a significant change in the proportion of TTR; as a result, it can be considered a clinically appropriate practice. This practice change did not seem to affect the incidence of acute GVHD or the incidence and severity of renal dysfunction. However, it has promoted patient convenience, has improved workloads of the transplant team and of pharmacists, and has yielded direct cost savings through a reduction in the frequency of sampling for tacrolimus measurements. Further studies with larger sample sizes and evaluation of the severity of acute GVHD in each patient would further validate these results.

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Standardization and Updating of a Drug Allergy Testing Program: The McGill Experience and Impact on Pharmacy Activities

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INTRODUCTION

Patients' claims of drug allergies are frequent but often not confirmed.[1] An unsubstantiated drug allergy label on a patient's chart can have a significant impact on clinical management. Retrospective studies have revealed that 3% to 6% of admissions to health care institutions are for unpredictable drug reactions, including drug allergies.[2] The consequences of unresolved drug allergy claims for patient care are substantial, including treatment delays, use of suboptimal treatment, longer hospital stays, and greater risks of complications.[3-7]

Drug allergy testing is effective for "de-labelling" individuals with suspected drug allergies; however, testing methods have often varied between, and even within, health care institutions. Until 2017, there was variability in testing protocols used in the McGill University Health Centre (in Montréal, Quebec). Variations between physicians were high, and the protocols were derived using available literature and were not always updated.[8,9] Allergists used sequential challenge doses set between 2- and 10-fold increments given at variable times (typically 30–45 min between challenge doses).[8-13] The lack of standardization made it difficult for the pharmacy to provide efficient compounding and clinical support. Literature comparing the various protocols was not available, which made it difficult for the pharmacists to either accept or reject the doses of prescriptions as written. It was clear that local policies and drug allergy testing algorithms had to be either created or updated. A comprehensive, focused drug evaluation program was inaugurated. Critical to implementation of the initiative was the creation of an allergist-pharmacist team to develop standard operating procedures, consensus-based uniform testing protocols, documentation forms, predefined prescriptions, and reports.

A critical component of any drug allergy evaluation is risk management. To that end, a drug allergy risk assessment tool was developed and its application made mandatory before any allergy testing. This tool had the dual aims of not only avoiding the testing of patients with absolute contraindications to drug challenge, but also identifying patients who could undergo single-dose, low-risk challenge.

This manuscript outlines the steps taken to establish the new drug allergy testing program and describes the subsequent positive impact in terms of streamlining pharmacy activity and improving patients' access to drug allergy testing.

DESCRIPTION OF THE DRUG ALLERGY PROGRAM

The Division of Allergy and Clinical Immunology at the McGill University Health Centre provides quaternary care and conducts research on and teaching about drug allergy. On average, 6000 patients with potential allergy (to drugs as well as food) are evaluated annually. The drug allergy screening program was gradually modified and fully implemented in 2017. As such, allergy testing transitioned from a physician-specific clinic to a program offered every day of the week, independent of the physician. Originally, prescriptions for testing of the same suspected drug allergy varied among physicians, and extensive compounding was required. To demonstrate these differences, 93 prescriptions for allergy challenge were reviewed; from these, the 5 oral medications with the most prescribing variability were identified. The prescriptions for these 5 medications, written by 8 physicians, revealed no consistent prescribing patterns (Table 1). The approach for drug allergy testing was to perform skin tests and then perform a graded drug challenge if appropriate.

Table 1. Prescribing Variations within and between Physicians for 5 Most Commonly Prescribed Drugs Tested for Allergies before 2011

	Drug Tested; Variant Prescription Sequences for Allergy Challenge				
Physician	**ASA**	**Celecoxib**	**Ibuprofen**	**Moxifloxacin**	**Penicillin V**
1	NA	1, 10, 30, 60 mg 2, 10, 50, 100 mg plus 5 × placebo 10, 30, 60 mg 2, 5, 10, 25 mg plus 4 × placebo 1, 50, 50, 100 mg plus 2 × placebo	2, 4, 20, 100 mg	NA	NA
2	15, 25, 100, 325 mg plus 2 × placebo 1, 81 mg plus 1 × placebo 25, 50, 100, 200, 325 mg 5, 50, 100, 325 mg	2, 20, 200 mg 20, 200 mg 20, 200 mg 1, 20, 200 mg	0.2, 2, 20, 200 mg 0.2, 5, 50, 200 mg plus 2 × placebo	0.4, 4, 40, 400 mg plus 1 × placebo	3, 30, 300 mg plus 2 × placebo 3, 30, 300, 300 mg 100, 200, 300 mg plus 1 × placebo
3	32.5, 325 mg 20, 40, 325 mg 1, 5, 10, 20, 80, 160, 325 mg plus 1 × placebo	20, 200 mg	40, 400 mg	40, 400 mg	30, 300 mg
4	5, 325 mg plus 1 × placebo 1, 5, 80, 160, 325 mg	NA	5, 10, 25 mg	400 mg plus 4 × placebo 4, 40, 200 mg plus 8 × placebo	NA
5	3.25, 32.5, 325 mg 1, 10, 100 mg	NA	NA	400 mg	30, 300 mg 300 mg
6	NA	2, 4, 10, 80, 100 mg plus 5 × placebo 20, 200 mg plus 2 × placebo	NA	NA	NA
7	NA	NA	NA	NA	100, 200, 300 mg 100, 200, 300 mg 300 mg
8	325 mg	NA	NA	NA	300 mg

NA = not applicable (allergy testing for this drug was not prescribed by the particular doctor).

Most allergists independently assessed and tested their own patients without sharing their protocols. To meet the increased demand for testing and to optimize pharmacist support without additional resources, the interdisciplinary team created a novel tool, established clear policies, attained protocol consensus, and generated standardized procedures. Following this standardization, drug challenges were conducted daily, and supervision of the challenges was pooled among allergists to allow flexibility in booking. The institutional research ethics board determined that the study was acceptable, but formal ethics approval was not required.

POLICIES AND PROCEDURES

On the basis of published guidelines, the emerging literature.[14,15] and the allergists' clinical experiences, an internal algorithm was drafted (Figure 1). Policies and standard operating procedures were then developed. The policies defined the roles of clinic physicians, pharmacists, and allergy nurses in conducting challenge and desensitization of suspected drug allergies. They also established specific safe venues for the testing to be done, human resources, and conditions for safe performance of the tests. Table 2 lists and briefly describes the documents generated. Existing reports and consent forms were reviewed and improved to be more informative.

A local risk assessment tool was also developed for use in patient triage, whereby patients with suspected drug allergy were stratified according to risk. The triage tool ensured uniformity in risk assessment by all allergists, eliminating patients at high risk for anaphylactic or other serious reactions. The nature of the challenge (single dose or multiple doses) was thus better defined, which enabled the pharmacy to have a consistent approach to compounding protocols while keeping the protocols specific for each drug. With this standardization, physicians could cross-supervise drug challenges ordered by their colleagues. The shared evaluation document led to rapid sharing of historical information by both the nursing staff and the allergist supervising the procedure. Since this study was conducted, an electronic version of the risk assessment tool has been developed (examples of such tools for penicillin are available in the literature and can also be used for other drugs[16]). Additional information about both the original tool and the newer electronic version are available, upon request to the corresponding author, to other institutions that are interested in developing their own tools.

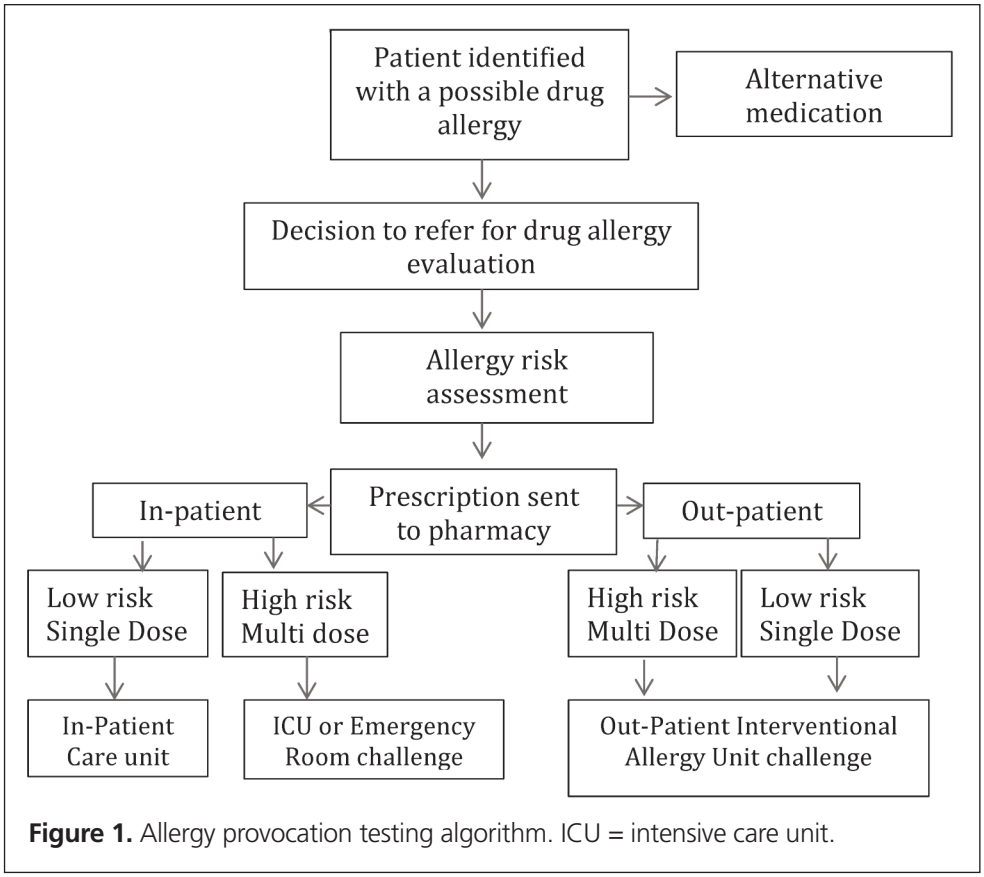

Figure 1. Allergy provocation testing algorithm. ICU = intensive care unit.

For drug provocation, doses for the "higher-risk" patients were limited to 1%, 10%, 30%, and 100% of the recommended single drug dose. Observation times for oral drugs before administration of the next dose remained at 30–45 min. All patients were monitored for at least 1 h after receiving the last dose of the sequence. For lower-risk patients, a single dose of a commercially available formulation was administered, either as an entire tablet or as a capsule. If a "blinded" dose was requested, a crushed drug preparation was placed in an empty capsule. Compounding was performed according to provincial requirements, using only drugs licensed by Health Canada.

A prescription was required for each challenge. Prescriptions were sent to the pharmacy and individually documented. The drugs identified as those most commonly tested as a single dose were provided as floor stock and registered retrospectively in the database. Other, less common drug requests for single and compounded preparations were sent to the clinic upon the patient's arrival. All suspected drug allergies were entered in the allergy module of the electronic medical record (EMR) and flagged until testing occurred with the comment "suspected allergy, as per allergy testing request, results pending".

The tests were performed either in a dedicated interventional outpatient allergy facility or on an inpatient care unit. If no adverse reaction was observed after the last dose, the patient was discharged home and asked to call the next day to report any late reactions. Current literature and guidelines suggested that multiple sequential doses on the same day could lead to desensitization rather than providing diagnostic information.[8,14] Therefore, the daily number of testing doses was limited to a maximum of 2 (not including placebo). The evaluation and all testing were carried out under the direct supervision of trained allergists.

EVALUATION OF THE PROGRAM

Pharmacy compounding records were used to review prescribing patterns before and after program initiation. Pharmacy resource utilization was assessed using variables captured in the database, including the number of prescriptions, the drugs and doses requested, and pharmacy activities related to the drug testing program. To estimate and normalize the compounding activities, the monthly number of doses dispensed was divided by the number of prescriptions, and the ratio of doses per prescription was obtained. The results were compared for the same 12-month calendar period before standardization (July 2014 to June 2015) and after full standardization (July 2016 to June 2017). The 12-month transition period (July 2015 to June 2016) was excluded to eliminate any carry-over effect.

RESULTS

Patients were tested for a total of 128 drugs, most belonging to the antibiotic and nonsteroidal anti-inflammatory drug

Table 2. Documents Related to Drug Allergy Testing Reviewed or Newly Created

Document	Description	Status
Policies		
Allergy provocation testing	Guidance in all aspects of allergy provocation (clarifies who can test and where)	New document
Drug desensitization	Guidance in all drug desensitization (clarifies who can desensitize and where)	New policy
Mandatory risk assessment before provocation testing	Policy to ensure that a specific risk assessment is performed before testing	New policy
Standard operating procedures		
Main standard operating procedure	General description of the department activities	New document*
Standard operating procedure for allergy provocation testing	General description of provocation testing	New document*
Preoperative operating procedure for drug allergy	General description of the pre-op ß lactam allergy testing	New document*
Desensitization procedures	General description for desensitization	New document*
Standard operating procedure for skin and intradermal allergy testing	General description for skin testing	New document*
Patient information documents		
Patient instructions for provocation test	Information to patient	Updated document
Consent form for food and /or drug provocation testing	Consent form	Updated document
Standard pharmacy prescriptions		
Pharmacy prescription for drug provocation testing	Standard preprinted prescription	New document
Pharmacy prescription for allergy testing prick test / intra dermal	Standard preprinted prescription	New document
Pharmacy prescription for desensitization and rescue medication	Standard preprinted prescription	New document
Nursing orders		
Before and after provocation testing	Standard preprinted order	Updated
For desensitization	Standard preprinted order	Updated
Reporting forms		
Pre drug provocation testing risk assessment	Standard preprinted prescription	New document
Provocation test result	Standard preprinted form	Updated
Nursing reporting form for food and drug provocation	Standard preprinted form	Updated
Physician reporting of drug provocation test	Standard preprinted form	Updated

*Previously based on published papers and/or case reports, specific to each physician.

(NSAID) classes. Penicillin V emerged as the most frequently prescribed medication (30% of prescriptions before and 32% of prescriptions after standardization), followed by amoxicillin (6% before and 15% after standardization). Other antibiotics with frequent requests for allergy testing included ciprofloxacin, azithromycin, clindamycin, and sulfamethoxazole-trimethoprim. However, the latter accounted for fewer than 20 prescriptions per year both before and after standardization.

In the second most frequently tested category of drugs, the NSAIDs, ibuprofen, acetylsalicylic acid, celecoxib, and naproxen together accounted for 18% and 13% of annual prescriptions before and after standardization, respectively.

Following standardization, several changes were noted. The annual number of prescriptions increased (from 478 for January to December 2015 to 748 for the same time frame in 2017), a 56% increase. Figure 2 details the monthly volume of prescriptions before and after standardization. The average number of doses per prescription was reduced, and the dose-to-prescription ratio declined from 2.04 to 1.47 (2-tailed t test, $p < 0.001$). The total annual quantity of doses required remained steady, at about 1050, while the proportion of single doses, using commercially available formulations, increased from 7% to 33%. In the first 6 months of 2019, the pharmacy dispensed 595 prescriptions for the purpose of allergy testing, of which 315 (53%) were dispensed as single-dose challenges.

After standardization, 4 possible dosages were available for predefined prescriptions: 1%, 10%, 30%, and 100%. The drug allergy testing was performed most commonly as single or 2 divided doses of 10% and 100% in a single-day challenge protocol. The 1% dose was rarely used, and less than 10% of all prescriptions involved a request for a 30% dose.

The infrastructure to support drug allergy testing consisted of a single pharmacist and a single technical assistant. Both of these individuals also supported the pharmaceutical research and special access programs. After-hours support for drug allergy testing continues to be limited to inpatients and is handled by the after-hours pharmacy distribution team. Standardization led to development of simpler compounding procedures that permitted easy accessibility after hours. Following standardization there was no increase in personnel to support the drug allergy testing program, despite the monthly increase in volume of prescriptions.

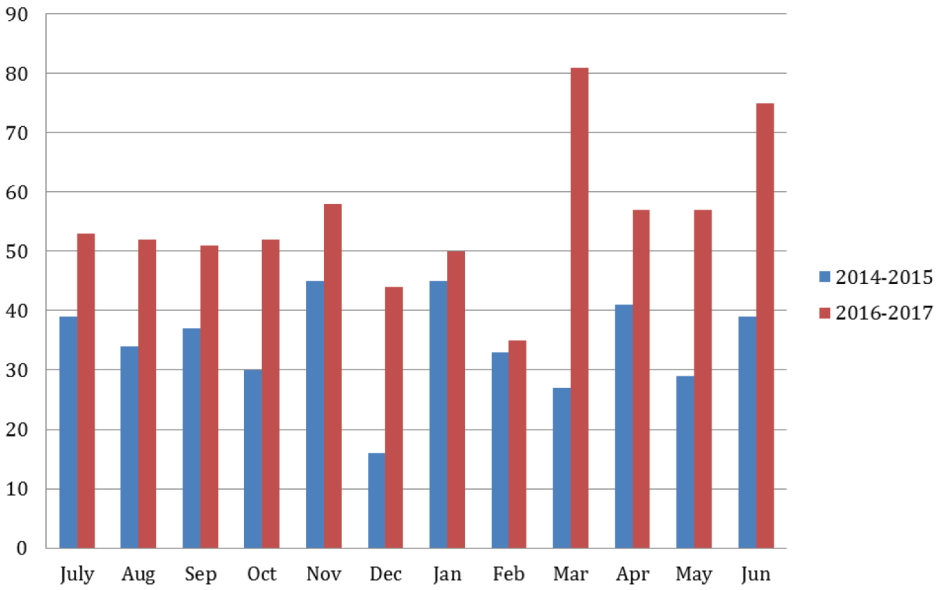

Figure 2. Number of monthly prescriptions filled before and after standardization.

DISCUSSION

The importance of unresolved drug allergies in clinical care is well known, and the negative impact of such allergies during hospitalization has been extensively discussed. Most concerns regarding drug allergy pertain to antibiotics.[5-7,14,17-23]

Before the establishment of the drug allergy evaluation program at the study hospital, variability in physicians' approaches to drug allergy testing was identified. To optimize the service, activities were reviewed, with the aim of integrating pharmacy and allergy-related activities. It was agreed that a consensus-based, standardized, and transparent approach would be beneficial. This approach represented a major change in culture and required improved interdisciplinary collaboration and pooling of allergist resources. Recent literature has echoed the need for such multidisciplinary teams and systematic standardized approaches in evaluating suspected drug allergies.[20]

In the field of drug allergy testing, 2 important objectives are to achieve diagnostic accuracy and to maintain maximum safety. Guidelines helped to ensure safety and provided direction for standardization. Literature comparing the validity of various doses is limited and has been generated from retrospective data.[14] About 10% of the general population claims to have an allergy to penicillin, yet more than 90% of these claims are eventually determined to be false.[24] Because of the high prevalence of suspected drug allergy, it was important to develop a rapid yet safe triage process to both minimize risk and optimize workload. The rapid identification of patients with low probability of drug allergy was a key factor in optimizing pharmacy activities and in shortening evaluation time at the clinic. The triage tool and the standard operating procedures have been essential to these changes.

Workflow streamlining occurred primarily through a shift to use of single-dose challenges, accomplished by application of the triage (risk assessment) tool by all physicians. Application of this tool reduced the time required to conduct testing from 4 h to 90 min for patients at lower risk of a reaction. The ability to conduct more challenges per day and the inherent great increase in the number of prescriptions was offset by the availability of on-site bulk drug dispensing. This shift to single-dose testing improved patients' access by doubling or possibly tripling the number of patients tested daily. Monitoring pharmacy activities allowed us to identify the needs of the drug allergy clinic and to optimize pharmacy support by determining the drugs and doses most frequently used.

Several additional benefits emerged from this practice update. Using the risk assessment tool, allergists were able to cross-supervise drug challenges. The interchangeability of physicians to perform the evaluation and testing, as well as protocol simplification, facilitated the daily operation of multiple drug allergy clinics, including a clinic for general drug testing and a clinic specific for preoperative penicillin allergy "de-labelling". The number of half-day clinics per week increased from 2 to 6. Standardization also provided a more robust method to evaluate the impact of drug allergy testing on clinical outcomes and knowledge transfer.[25] Optimizing the prophylactic use of antibiotics in surgery improved operating room efficiency.[22] These encouraging results led to plans to extend testing to other regional health care centres and to target specific units with high rates of adverse reactions to drugs, such as the dialysis and oncology units.

With any such expansion of the program, it will be necessary to reassess supporting pharmacy infrastructure. Through this program, we have identified a need to document clinical outcomes following de-labelling as part of a quality assurance platform. Quality improvement should go beyond assessing repeat drug exposure after de-labelling. It must include communication and reporting issues, safety assessment, and impact on long-term patient care.

Simplification and standardization of the allergy assessment were critical to the success of the program. Close interdisciplinary collaboration was important to minimize the impact on resources. The pharmacy infrastructure to support the allergy clinic was assigned to an existing pharmacy research department. Although the institution's department of pharmacy offers services to 3 sites, only one of these sites provides full allergy support. Specifically, one pharmacist and one pharmacy technical assistant at the Montreal General Hospital site of the McGill University Health Centre are assigned to support a sector that includes clinical drug research, management of drugs in the special access program, and provision of drug allergy testing. Following standardization, there was no increase in personnel to support the drug allergy program. Instead, there has been improved human resource utilization, which can be attributed to the simplification and standardization process that we employed.

An unexpected benefit of this quality improvement program was the review of internal and external pharmacy communication. The pharmacy record uniquely identified each patient and comprehensively documented details of the drug used in the challenge. Although the physician's report of the testing outcome was scanned and entered in the EMR, the drug allergy flag was not simultaneously removed from the EMR in all cases. All prescriptions were in a non-EMR pharmacy database, which allowed for rapid identification of those tested. The availability of duplicate documentation across databases proved useful as a means of identifying those instances where full de-labelling of the patients by the physicians was not completed in the EMR. This duplicate information may prove useful in developing a quality assurance program. Knowledge transfer relating to allergy labels has been identified as suboptimal in many institutions, including ours.[6,22,25]

There was a need to create a simple version of the final, allergist-certified report in the EMR, in addition to the source challenge documents. The above findings echo recommendations of others in the recent literature.[6,26] Further improvements in communication are necessary, including uniform reporting terminology and systematic transmission to community physicians and pharmacists of information about patients with successful de-labelling of drug allergies. Given the current high prevalence of suspected drug allergy, a multi-hospital approach may be necessary,[23] with the establishment of an integrated program involving the broad community of health care professionals, including community pharmacists.[6]

CONCLUSION

The safe administration of drugs is a prerequisite for excellence in patient care. It necessitates clarification of patients' drug allergy claims before drug administration. Standardizing and updating drug allergy testing had a beneficial effect on pharmacy compounding activities and led to improvement in patients' access to testing. The volume of prescriptions and the number of patients tested for drug allergy have increased substantially without any need for extra pharmacy staffing or equipment.

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ON THE FRONT COVER

Footprints in the Snow
Carp Ridge, Ottawa, Ontario

Amanda Iannaccio took this picture in rural Kanata in February 2018 with her iPhone 8. The photo captures Carp Ridge, a small range of rocky hills above the Carp Valley, one of the largest environmentally significant areas within the National Capital region. Amanda, who is CSHP's Content Officer, has been working in publishing for a decade and has been coordinating the publication of the *Canadian Journal of Hospital Pharmacy* for the past 5 years. She enjoys long walks in nature, listening to jazz on vinyl, and visiting wineries with her husband in their spare time.

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

Programme PLUSRx : Pharmacothérapie liée à l'utilisation sécuritaire des médicaments

par Pauline Rault, Amélie Duhamel, Dana Necsoiu, Isabelle Desjardins, Denis Lebel et Jean-François Bussières

INTRODUCTION

Avec l'entrée en vigueur de la réglementation entourant la Loi de Vanessa, les établissements de santé du Canada et les départements de pharmacie de ces établissements sont contraints de respecter cette nouvelle exigence[1,2]. Entrée en vigueur en 2019, cette modification législative oblige tout établissement de soins de santé de fournir en bonne et due forme au ministre, dans les 30 jours suivant la consignation par l'hôpital des médicaments incriminés et selon les modalités réglementaires, les renseignements sur les réactions indésirables graves à une drogue, qui relèvent de l'autorité ministérielle[3]. Les réactions indésirables à une drogue sont jugées graves si elles entrainent une malformation congénitale, une invalidité, une incapacité, une mise en danger ou la mort.

Bien que le pharmacien soit un expert du médicament, la pharmacovigilance ne présente qu'une seule dimension de ses activités professionnelles. Dans le rapport sur les pharmacies hospitalières canadiennes de 2016-2017, on note la participation du pharmacien à des activités de surveillance et à la déclaration des effets indésirables aux médicaments (EIM) dans 71 % (131/184) des établissements. Toutefois, seulement 21 % (39/184) des établissements le font dans tous leurs secteurs de soins. En outre, 41 % (58/141) des établissements de soins de santé s'appuient sur le travail des techniciens en pharmacie pour aider à réunir les données à présenter au comité de pharmacovigilance[4]. Les données canadiennes indiquent une couverture partielle en matière de pharmacovigilance. L'absence de structure qui cadre avec la pharmacovigilance n'encourage pas les pharmaciens hospitaliers à effectuer la notification des EIM à Santé Canada.

Au sein de notre établissement, l'équipe du Département de pharmacie a mis en place en 2006 un programme structuré de pharmacovigilance (PLUSRx – pharmacovigilance liée à l'utilisation des médicaments). Dans la foulée des changements législatifs, nous pensons qu'il est utile de faire connaitre ce programme afin de soutenir les départements de pharmacie au Canada.

Il s'agit d'une étude descriptive transversale. L'objectif principal était de décrire et d'évaluer l'ensemble des activités du programme PLUSRx mis en place au Centre hospitalier universitaire (CHU) Sainte-Justine.

DESCRIPTION DU PROGRAMME

Le CHU Sainte-Justine est un centre hospitalier universitaire mère-enfant de 500 lits. L'établissement compte un effectif de 36,4 équivalents-temps-plein pharmaciens (ETP) ou 40 pharmaciens employés par l'établissement, de 50 ETP assistants techniques séniors en pharmacie et de quatre résidents en pharmacie hospitalière chaque année.

Depuis le milieu des années 1990, nous avons progressivement ajouté des pharmaciens en les décentralisant dans les programmes de soins hospitaliers et certains programmes de soins ambulatoires afin de prodiguer des soins pharmaceutiques complets. Ce type de soins comporte notamment la prévention et la gestion des EIM en collaboration avec les médecins, les infirmières et surtout le patient. Cette transition vers les soins offerts aux patients a contribué à limiter l'intérêt pour les fonctions transversales de la part des jeunes pharmaciens diplômés qui ont été embauchés. Malgré cet attrait pour les soins, qui a permis à un plus grand nombre de patients de profiter des services du pharmacien dans la gestion des EIM, la déclaration à Santé Canada est restée limitée, compte tenu de la priorité accordée à l'activité de notification et le temps dont disposee l'équipe de pharmacovigilance. C'est pourquoi, dès 2006, nous avons choisi de structurer progressivement un programme transversal de soutien à la pharmacovigilance. Le programme PLUSRx a d'abord été bâti autour de résidents en pharmacie (volet international) sous la supervision de pharmaciens dans le cadre d'une résidence en

pharmacovigilance de 12 mois. Durant quelques années, cette résidence était offerte à des internes en pharmacie hospitalière de France. Leur contribution a permis de structurer l'activité. Aujourd'hui, le Programme repose sur une équipe pluridisciplinaire constituée de deux ETP (détentrices d'un baccalauréat en sciences biopharmaceutiques). Ces ressources sont financées en partie par l'établissement et le reste du financement est pris en charge par le Canadian Pharmacogenomic Network for Drug Safety (CPNDS [Réseau canadien de surveillance en pharmacogénomique]). Cette équipe œuvre sous la responsabilité du pharmacien-chef adjoint aux soins, à l'enseignement et à la recherche. Elle collabore avec tous les pharmaciens du Département, l'équipe de la Direction qualité-risque et le Service des archives médicales (deux archivistes sont en relation directe avec l'équipe de pharmacovigilance).

De plus, la mise en place du programme PLUSRx a également permis de participer au CPNDS qui mène différents projets de recherche visant à déterminer des polymorphismes prédicteurs d'EIM chez les enfants[5].

Ainsi, au cours des dix dernières années du Programme, l'équipe de soutien à la pharmacovigilance a déclaré localement 1068 EIM. La figure 1 présente le profil du nombre de déclarations locales d'EIM, du nombre de déclarations d'EIM à Santé Canada et du nombre de patients recrutés dans le programme CPNDS du 1er avril 2008 au 31 mars 2019. De plus, une majorité (74,3 %, 794/1068) de ces EIM a été rapportée à Santé Canada. Dix rapports de cas ont été publiés dans la littérature pharmacologique. En outre, durant cette même période, 36 228 activités de type « pharmacovigilance » ont été réalisées par les pharmaciens décentralisés dans les programmes de soins, ce qui correspond à environ neuf interventions de pharmacovigilance par jour. Une activité de pharmacovigilance correspond à une action de détection d'un EIM par le pharmacien ou à sa prise en charge (p. ex. modification de posologie d'un médicament, substitution par un autre médicament, aide à la gestion des conséquences cliniques de l'EIM, etc.); elle peut également impliquer une déclaration locale ou à Santé Canada. On s'attend à ce qu'une majorité des activités de pharmacovigilance comptabilisées par le journal de bord et réalisées par les pharmaciens visent à prévenir la survenue des EIM et à en assurer la prise en charge, et un nombre limité de ces activités mènent à une déclaration d'EIM graves faite à Santé Canada. La figure 2 présente le profil du nombre d'activités de pharmacovigilance (c.-à-d. EIM évités ou pris en charge) par les pharmaciens cliniciens dans les différents programmes de soins au CHU Sainte-Justine du 1er avril 2008 au 31 mars 2019. De plus, de nombreux travaux de recherche ont été menés localement afin de mieux comprendre les caractéristiques des EIM à déclarer et leur gestion[6-10].

ÉVALUATION DU PROGRAMME

En 2019, nous avons mené une évaluation du programme PLUSRx auprès des pharmaciens du Département de pharmacie de l'établissement. Elle visait à vérifier auprès des pharmaciens leur connaissance du Programme et à recueillir leurs commentaires. Un sondage en ligne (Surveymonkey, San Matteo [Californie]) a été élaboré par l'équipe de recherche (CHU Sainte-Justine). Il comportait deux parties, soit le profil des répondants (nombre d'années d'expérience du répondant, domaine d'expertise et nombre d'EIM auxquels il a été confronté durant la dernière année financière [2018-2019]) et la mesure de la satisfaction des pharmaciens relative aux activités du programme PLUSRx. L'échelle de Likert utilisée à cet effet comptait cinq choix (totalement satisfait, partiellement satisfait, partiellement insatisfait, totalement insatisfait et non applicable pour ceux qui ne connaissaient pas l'existence de l'activité en question).

Les investigateurs ont reçu les réponses de 29 pharmaciens (29/37, 78 %). Quinze (15/29, 52 %) d'entre eux exerçaient au CHU Sainte-Justine depuis plus de 10 ans. Les pharmaciens ayant

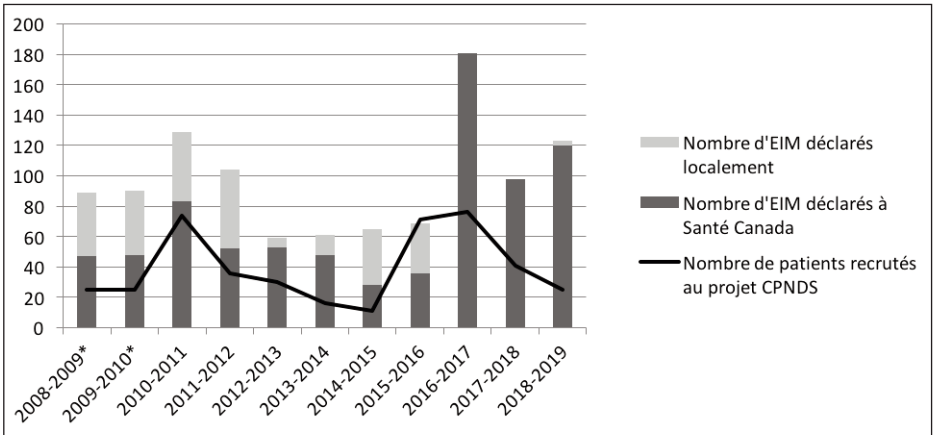

Figure 1. Profil du nombre de déclarations locales d'effets indésirables médicamenteux (EIM), du nombre de déclarations d'EIM à Santé Canada et du nombre de patients recrutés dans le programme CPNDS (Réseau canadien de surveillance en pharmacogénomique) du 1er avril 2008 au 31 mars 2019.

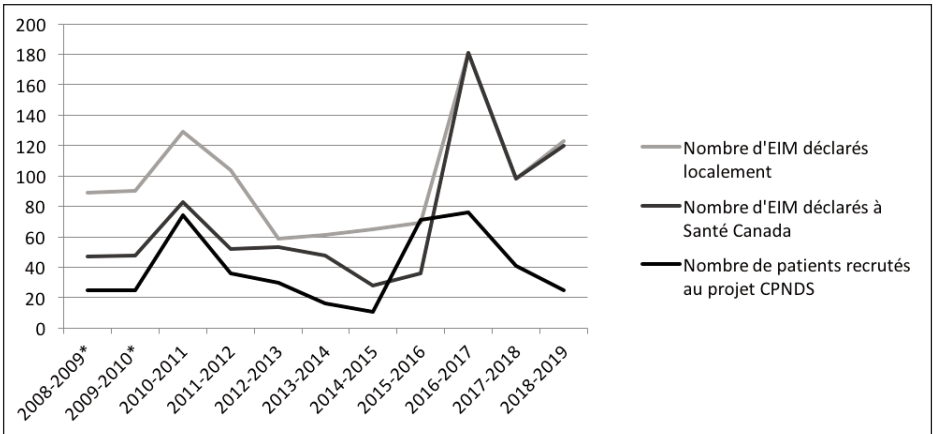

Figure 2. Profil du nombre d'activités de pharmacovigilance (c.-à-d. effets indésirables médicamenteux [EIM] évités ou pris en charge) par les pharmaciens cliniciens dans les différents programmes de soins au CHU Sainte-Justine du 1er avril 2008 au 31 mars 2019.

répondu provenaient de l'équipe de pédiatrie (12/29, 41 %), d'hémato-oncologie (4/29, 14 %), de mère-enfant (5/29, 17 %) et de l'équipe de gestion (8/29, 28 %). Au cours de l'exercice de 2018-2019, les pharmaciens ont dit avoir été exposés à une médiane de neuf EIM graves et avérés à l'étage (min. : 0; max. : 2000), à aucun EIM grave à l'étage (min. : 0; max. : 250) et ont participé à la déclaration d'une médiane d'un EIM (min. : 0; max. : 10). Les pharmaciens ont toutefois participé à un grand nombre d'activités visant à prévenir la survenue d'EIM ou à assurer la prise en charge d'EIM sans gravité. Le tableau 1 présente un profil chronologique croissant des activités du programme PLUSRx ainsi que le degré de satisfaction des pharmaciens vis-à-vis de chacune des activités.

DISCUSSION

Cette étude descriptive présente un programme original de pharmacovigilance (PLUSRx) géré par des pharmaciens hospitaliers dans un établissement de santé au Canada.

Dans la littérature canadienne, il n'existe pas d'exemples similaires qui présentent un programme global incluant une variété d'activités de soins et de soutien. Toutefois, plusieurs études confirment la capacité des pharmaciens à prévenir, déceler et prendre en charge ou à déclarer les EIM et, au cours des dernières années, la littérature démontre un intérêt croissant entourant l'évaluation de tels programmes. Par exemple, He et collab.[13] ont démontré l'intérêt de décentraliser les pharmaciens dans les équipes de soins tertiaires et de les faire participer aux tournées de patients afin d'accroître la détection et la déclaration des EIM. Van Grootheest et de Jong-van den Berg[14] ont commenté la contribution essentielle des pharmaciens hospitaliers et communautaires à la prévention, à la prise en charge et à la déclaration des EIM aux Pays-Bas. Phansalkar et collab.[15] ont mené une méta-analyse portant sur 13 études. Elle confirme la supériorité des pharmaciens par rapport à d'autres professionnels (c.-à-d. médecins, infirmières et archivistes médicaux) pour la détection rétrospective d'EIM à partir de dossiers patients[15]. Yu et collab.[16] se sont intéressés aux EIM sévères détectés dans un hôpital pédiatrique de janvier 2011 à septembre 2014. Les auteurs ont mis en évidence un programme de pharmacovigilance placé sous la responsabilité des pharmaciens, ayant permis la détection de 166 EIM graves survenus chez 163 patients. Morales Ríos et collab.[17] ont décrit un programme hospitalier de pharmacovigilance dans un établissement pédiatrique du Mexique, ayant eu un impact positif sur la détection et la déclaration des EIM. Leur programme a permis la transition de la déclaration des EIM d'un système papier à un système informatisé plus efficient[17]. Notre étude illustre la faisabilité d'implanter et de maintenir un programme de pharmacovigilance qui soutienne la prestation de soins pharmaceutiques offerts par les pharmaciens cliniciens dans les programmes de soins. Le Programme est original, notamment avec l'arrimage de la pharmacie au service des archives et les nouvelles stratégies de codification des EIM, la détermination des bonnes pratiques et la mise en place d'une communauté de pratique au Québec.

La description de notre programme met en évidence une hausse du nombre d'EIM décelés, déclarés localement et à l'autorité réglementaire parallèlement à l'augmentation du nombre d'activités mises en place dans le cadre du Programme. Toutefois, nous avons atteint un plateau depuis quelques années. Terblanche et coll. ont démontré l'impact favorable d'un tel programme sur les pratiques de déclaration des EIM (c.-à-d. hausse de 12,1 % à 33,8 % des professionnels de la santé concernés par au moins une déclaration d'EIM) après la mise en place d'un programme de pharmacovigilance géré par les pharmaciens[18]. Guédat et collab.[19] ont rapporté également une hausse (jusqu'à 10 fois) de la déclaration des EIM avec la mise en

Tableau 1 (partie 1 de 2). Profil chronologique croissant des activités du programme de pharmacovigilance PLUSRx ainsi que le degré de satisfaction des pharmaciens vis-à-vis de chacune des activités

		Satisfaction vis-à-vis du programme PLUSRx, nombre (%) des pharmaciens (*n* = 29)		
Date de mise en place	**Description de l'activité**	**Satisfait**	**Insatisfait**	**Ne connaît pas l'activité**
Fin 1990	Présence de pharmaciens cliniciens au sein des programmes de soins - Des pharmaciens ont été ajoutés à tous les programmes de soins au cours des deux dernières décennies ; tous les patients hospitalisés profitent maintenant de soins pharmaceutiques et certaines patientèles ambulatoires bénéficient d'une prévention et prise en charge des EIM.	23 (79)	1 (3)	5 (17)
Janvier 2006	Identification d'un coordonnateur de pharmacovigilance - Création de la fonction de coordonnateur de pharmacovigilance qui coordonne toutes les activités mises en place pour promouvoir et soutenir la pharmacovigilance auprès des équipes de soins. - Outre les missions décrites dans ce tableau, le coordonnateur est la personne ressource de la pharmacie en termes de pharmacovigilance, centralisant l'information.	25 (86)	2 (7)	2 (7)
Janvier 2006	Lien téléphonique privilégié - Création d'une ligne téléphonique spécifique à la pharmacovigilance (poste 3636), avec une messagerie disponible en tout temps. - Cette ligne permet un contact direct du personnel soignant avec le coordonnateur de la pharmacovigilance pour toute question relative à la pharmacovigilance et à la déclaration des EIM à Santé Canada.	24 (83)	0 (0)	5 (17)
Janvier 2006	Plateforme de pharmacovigilance sur l'intranet - Mise en place d'une section consacrée à la pharmacovigilance sur l'intranet de la pharmacie. - Cette plateforme accessible à tout le personnel soignant informe sur les modalités de déclaration à Santé Canada et renvoie vers des documents utiles en pharmacovigilance.	12 (41)	2 (7)	15 (52)
Janvier 2006	Une base de données regroupant les EIM déclarés à Santé Canada - Base de données locales de collecte des EIM permettant de suivre les déclarations internes au CHU Sainte-Justine et de réaliser des bilans mensuels et annuels diffusés au personnel de la pharmacie et de générer un rapport de déclaration pour Santé Canada à partir des données colligées. - Création d'un fichier Excel pour le suivi des déclarations à Santé Canada par mois et par année.	15 (52)	4 (14)	10 (34)
2006	Arrimage externe en pharmacogénomique - Participation du CHU Sainte-Justine au CPNDS de Vancouver afin de faciliter l'identification les patients victimes d'EIM et les patients « témoins » en vue de séquencer leur ADN pour déterminer les polymorphismes prédicteurs d'EIM.	17 (59)	0 (0)	12 (41)
2007	Tournée périodique dans les services - Tournées périodiques du coordonnateur de pharmacovigilance dans les services cliniques afin de rencontrer l'infirmière assistante ou un pharmacien du service pour déterminer des cas potentiels d'EIM ou en discuter.	13 (45)	0 (0)	16 (55)
2008	Sous-comité et bilan annuel - Création d'un sous-comité de pharmacovigilance appartenant au comité de pharmacologie. - Présentation du rapport annuel des activités de pharmacovigilance à la fin de chaque année financière.	24 (83)	0 (0)	5 (17)
Décembre 2008	Surveillance des alertes externes - Le coordonnateur de pharmacovigilance est abonné aux alertes de Santé Canada et de la FDA concernant la sécurité des médicaments. - Sélection, tri et envoi des alertes pertinentes aux chefs médicaux des services concernés.	25 (86)	2 (7)	2 (7)

suite à la page 56

Tableau 1 (partie 2 de 2). Profil chronologique croissant des activités du programme de pharmacovigilance PLUSRx ainsi que le degré de satisfaction des pharmaciens vis-à-vis de chacune des activités

		Satisfaction vis-à-vis du programme PLUSRx, nombre (%) des pharmaciens (*n* = 29)		
Date de mise en place	**Description de l'activité**	**Satisfait**	**Insatisfait**	**Ne connaît pas l'activité**
2009	Rapports et publications - Rédaction et publication de rapports de cas sur des EIM décelés chez des patients du CHU Sainte-Justine en collaboration avec l'équipe soignante s'occupant de la prise en charge du patient.	24 (83)	1 (3)	4 (14)
2016	- Rédaction d'un article synthèse sur la démarche, dont un formulaire de consentement pour les patients			
Février 2016	Courriel mensuel sur les EIM locaux - Rédaction et envoi mensuels de bilans de pharmacovigilance à tous les pharmaciens. - Le bilan mensuel liste tous les EIM déclarés à Santé Canada au cours du dernier mois.	27 (93)	0 (0)	2 (7)
Novembre 2017	Arrimage avec le service des archives - Instauration d'une collaboration pérenne entre les archivistes médicaux et l'équipe de pharmacovigilance : ◦ Analyse bimensuelle des nouvelles données de codification des effets indésirables médicamenteux. ◦ Validation des EIM décelés et des codes utilisés. ◦ Caractérisation de la gravité des EIM. ◦ Comparaison des EIM graves décelés avec ceux de la base de données de pharmacovigilance. ◦ Déclaration à postériori à Santé Canada des nouveaux EIM graves décelés.	17 (59)	0 (0)	12 (41)
Septembre 2018	Delphi et bonnes pratiques de pharmacovigilance hospitalière au Québec[11,12] - Réalisation d'un Delphi en deux tours avec 25/30 chefs de département de pharmacie des établissements de santé du Québec. - Détermination de 37 bonnes pratiques de pharmacovigilance en pharmacie hospitalière.	10 (34)	1 (3)	18 (62)
Décembre 2018	Communauté de pratique en pharmacovigilance au Québec - Mise en place d'une communauté de pratique regroupant les 30 départements de pharmacie hospitalière du Québec sous forme de conférences téléphoniques de 60 minutes. - Discussion axée sur la gestion de la pharmacovigilance. - Partage de documents et d'outils.	9 (31)	2 (7)	18 (62)
Janvier 2019	Politiques et procédures - Rédaction et mise à jour de politiques et procédures (p. ex. programme de la pharmacovigilance, collaboration entre les archives et la pharmacie)	16 (55)	1 (3)	12 (41)

CHU = Centre hospitalier universitaire, CPNDS = Canadian Pharmacogenomics Network for Drug Safety (Réseau canadien de surveillance en pharmacogénomique), EIM = évènement indésirable médicamenteux, FDA = Food and Drug Administration (États-Unis), PLUSRx = Pharmacothérapie liée à l'utilisation sécuritaire des médicaments.

place d'un programme de pharmacovigilance dans un centre hospitalier universitaire en France. Un programme structuré peut contrer les barrières à la déclaration[20]. Dans notre centre, la présence de pharmaciens dans toutes les unités de soins a sans doute facilité la mise en place du programme PLUSRx. Il demeure toutefois possible d'implanter une structure centralisée favorisant la déclaration des EIM graves sans pour autant qu'il y ait une couverture en soins pharmaceutiques à l'échelle de l'établissement.

Bien que le Programme ait été mis en place progressivement depuis 2006, l'évaluation menée a montré la méconnaissance de quelques pharmaciens de certaines activités. On remarque que les étapes moins connues n'impliquent pas la participation directe du pharmacien. D'autres facteurs expliquent cette méconnaissance, notamment la rotation annuelle des résidents en pharmacie qui participent au Programme, l'inexpérience de certains répondants, l'importance accrue accordée à la prise en charge clinique des EIM, plutôt qu'à leur déclaration locale ou à Santé Canada ou encore l'implantation récente de certaines activités (p. ex. bonnes pratiques de pharmacovigilance, communauté de pratique). À la suite de cette évaluation, nous avons davantage abordé ce sujet en réunion et l'avons discuté afin de pallier la méconnaissance qu'ont certains pharmaciens de l'ensemble des activités de pharmacovigilance mises en place au sein de l'établissement.

Cette étude comporte des limites. Par exemple, elle ne décrit pas en détail les modalités de détection, d'analyse et de déclaration des EIM. Chacune de ces étapes comporte plusieurs modalités. La mise en place d'une communauté de pratique effectuée par notre équipe vise notamment à partager ces modalités afin d'élargir l'activité de pharmacovigilance à l'échelle du Québec.

CONCLUSION

Pour donner une suite à l'obligation faite aux établissements de santé au Canada de déclarer les EIM graves, cet article décrit un programme original et complet de pharmacovigilance en établissement de santé.

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For Primary Prevention, Should All Moderate- to High-Risk Patients Be Considered Candidates for Acetylsalicylic Acid?

THE "PRO" SIDE

Acetylsalicylic acid (ASA) was first investigated for use in primary prevention of cardiovascular disease in the 1980s.[1] Since that time, more than 160 000 individuals have participated in studies of ASA for primary prevention.[2] On the basis of available data, the American College of Cardiology/American Heart Association guidelines for primary prevention (2019) recommend that ASA be considered for prevention of atherosclerotic cardiovascular disease in patients deemed to be at high risk without elevated bleeding risk.[3] Similarly, the guidelines of Hypertension Canada (2020) and the Canadian Diabetes Association (2018) both recommend that ASA be considered to reduce vascular risk in these populations in the absence of elevated bleeding risk.[4,5]

In 2018, three large primary prevention trials comparing ASA with placebo were published (ARRIVE,[6] ASCEND,[7] ASPREE[8]). The ASCEND study, which compared ASA with placebo in participants with diabetes, found a statistically significant reduction in the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or vascular-related death) after a median of 7.4 years (8.5% versus 9.6%, $p = 0.01$).[7] In the ARRIVE and ASPREE studies, both of which compared ASA with placebo in primary prevention populations, trends toward benefit in the prevention of cardiovascular disease did not reach statistical significance.[6,9] At the same time, each of these studies found a statistically significant increase in the risk of bleeding with ASA, relative to placebo (for ARRIVE, 0.97% versus 0.46%; for ASCEND, 4.1% versus 3.2%; for ASPREE, 3.8% versus 2.8%).[6-9]

Some might interpret these data to mean that ASA should not be used for primary prevention; however, the lack of a statistically significant benefit in the ARRIVE and ASPREE studies must be considered in the context of the much lower than expected rate of cardiovascular outcomes. Over the 5-year duration of the ARRIVE study, the primary composite cardiovascular outcome (myocardial infarction, stroke, cardiovascular death, unstable angina, transient ischemic attack) occurred in 4.29% and 4.48% of participants randomly assigned to receive ASA and placebo, respectively, well below the originally expected event rates of 11.4% (ASA) and 13.4% (placebo).[6] Similarly, over the 4.7 years of the ASPREE study, the rates of the composite cardiovascular outcome (fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, hospital admission for heart failure) were 4.7% and 4.9% among participants randomly assigned to ASA and placebo, respectively.[8] Thus, the lack of benefit seen in these low-risk populations is not necessarily applicable to the population with moderate to high risk.

Multiple systematic reviews and meta-analyses incorporating these new data have been published, many of which highlight a benefit in prevention of nonfatal cardiovascular events at the cost of excess bleeding.[10] One such meta-analysis, performed by Zheng and Roddick,[2] found statistically significant reductions in the composite cardiovascular outcome (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke; absolute risk reduction [ARR] 0.41%, 95% confidence interval [CI] 0.23%–0.59%, number needed to treat [NNT] 241), myocardial infarction (ARR 0.28%, 95% CI 0.05%–0.47%, NNT 361), and ischemic stroke (ARR 0.19%, 95% CI 0.06%–0.30%, NNT 540). A greater reduction in the primary composite cardiovascular outcome was seen in the subgroups with high risk of cardiovascular disease (ARR 0.63%, 95% CI 0.18%–1.03%, NNT 160) and with diabetes (ARR 0.65%, 95% CI 0.09%–1.17%, NNT 153).[2] These benefits of ASA in higher-risk populations are on par with the benefits of statins when used for primary prevention, for which the NNTs for myocardial infarction, stroke, and cardiovascular death are 123, 263, and 233, respectively.[11] Not unexpectedly, the same meta-analysis found an increase in major bleeding (absolute risk increase [ARI] 0.47%, 95% CI 0.34%–0.62%, number needed to harm 210).[2]

Although direct comparison of the benefits and risks shows similar numeric values for ARRs and ARIs, the clinical significance of these events is not equivalent. The rate of fatal bleeding with ASA is extremely low (0.29% in the ASPREE study), as is the rate of disability following major hemorrhagic events.[9,12] In a prospective cohort analysis of bleeding events secondary to long-term antiplatelet use, the rate of disability after a bleeding event was estimated at 0.5%.[12] By comparison, in-hospital and 1-year mortality rates after acute myocardial infarction have been estimated at 4.0% and 7.6%, respectively, and hospital admission for heart failure at 4 years after acute myocardial infarction has been estimated at 12%.[13,14] After a stroke, the risk of in-hospital mortality has been estimated at 2%, and 10-year post-stroke disability rates have been estimated as 12.2% for moderate disability, 14.4% for severe disability, and 28.0% for cognitive impairment.[15,16] Thus, the differing clinical outcomes after cardiovascular and bleeding events must lead us away from interpreting these similar ARRs and ARI as equivalent.

Finally, patient preference plays an important role in treatment selection. Although few data are available on patient preferences regarding ASA for primary prevention, extensive data exist on patient preferences concerning antithrombotic agents for atrial fibrillation. A narrative systematic review found that patients with or without atrial fibrillation considered the outcome of disabling stroke worse than death. To prevent a single stroke, patients were willing to accept multiple serious bleeding events, with a reported acceptable range of

2 to more than 33 serious bleeding events per stroke prevented.[17] Thus, it is apparent that patients do not place equal value on cardiovascular events and bleeding events.

Overall, while ASA used in the primary prevention of cardiovascular disease appears to have a similar ARR for cardiovascular outcomes as its ARI for major bleeding, the cardiovascular outcomes are clinically more significant than the bleeding outcomes, and are valued as such by patients. ASA for primary prevention may not be appropriate for everyone, but it should be considered for all individuals at moderate to high risk of cardiovascular disease.

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THE "CON" SIDE

The efficacy of acetylsalicylic acid (ASA) for prevention of vascular events in patients with existing cardiovascular disease is well established.[1] Among those patients, the focus lately has been on the extent to which newer options (e.g., P2Y12 inhibitors, non–vitamin K antagonist oral anticoagulants) can augment or displace ASA.[2-5] In parallel, many large randomized controlled trials (RCTs) have investigated the benefits and harms of ASA in various primary prevention populations (patients without clinically manifest coronary heart disease, cerebrovascular disease, or peripheral artery disease). Meta-analyses of these trials have included more than 165 000 patients with over 1 million patient-years of follow-up and 3 large recent RCTs in populations about which there was residual uncertainty (patients with diabetes, the elderly, and those needing high-risk primary prevention).[6,7] If you believe, as I do, that RCTs are the most powerful methodology to detect cause-and-effect relationships between drugs and outcomes, then there is ample basis for confidence that the role of ASA in primary prevention is minor and diminishing.

Simply put, there is high-quality evidence that many primary prevention patient populations should *not* be considered candidates for ASA, including the following:

Primary prevention patients 70 years of age or older: The recent ASPREE trial showed that in patients 70 years or older, relative to placebo, ASA did not reduce cardiovascular events,[8] dementia, or physical disability,[9] caused major bleeds (hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.18–1.62, number needed to harm [NNH] 98 for 4.7 years), and increased all-cause mortality (HR 1.14, 95% CI 1.01–1.29, NNH 142 for 4.7 years), a major contributor to which was cancer death

(HR 1.31, 95% CI 1.0–1.56, NNH 137 for 4.7 years).[10] This trial, one of the largest RCTs ever conducted, strongly indicates that initiating ASA for primary prevention in people aged 70 years or older is inappropriate. It also raises the question of whether, for patients who start the drug at a younger age, ASA should be stopped when they reach that age. This choice should be based on the strength of the rationale for starting ASA in the first place, and the preponderance of current evidence discussed below indicates that the rationale is weak for most patient groups.

Primary prevention patients who are receiving anticoagulants: We now have solid evidence that ASA plus oral anticoagulant (OAC) causes more major bleeding than OAC alone, and the combination provides no additional benefit in patients with atrial fibrillation who have prior acute coronary syndrome.[4,11-14] It is even more difficult to justify ASA in anticoagulated patients with atrial fibrillation in the absence of coronary artery disease. In primary prevention, patients who do not have atrial fibrillation and who are receiving an anticoagulant for some other reason (e.g., venous thromboembolism) have increased risk of major bleeding with combined ASA and OAC. In addition, several trials showing that OACs prevent coronary events at least as effectively as ASA[15-17] imply that ASA causes net harm for patients who are taking an OAC for non–atrial fibrillation conditions. Antiphospholipid syndrome with arterial thrombosis is a notable possible exception to this.[18]

Many patients with diabetes: Previous trials showed lack of efficacy of ASA for primary prevention in patients with diabetes.[19,20] The recent ASCEND trial showed fewer serious vascular events (rate ratio 0.88, 95% CI 0.79–0.97, NNT 91 for 7.4 years) and excess major bleeding (rate ratio 1.29, 95% CI 1.09–1.52, NNH 112 for 7.4 years) with ASA relative to placebo.[21] Meta-analysis of all 7 trials of ASA in patients with diabetes revealed no benefit in terms of any specific efficacy outcome and clear evidence of harm (HR for major bleeding 1.29, 95% CI 1.11–1.51, NNH 120 for about 7 years; HR for major gastrointestinal bleeding 1.35, 95% CI 1.05–1.75, NNH 242 for about 7 years [where 7 years is the weighted mean follow-up duration combining JPAD, POPADAD, and ASCEND trials]).[6] Use of ASA for primary prevention in patients with diabetes is therefore likely to be a highly preference-sensitive decision.

For patients outside the categories for which ASA should probably be avoided, ASA offers the possibility of reducing the risk of nonfatal myocardial infarction (HR 0.85, 95% CI 0.76–0.95, NNT 366 for about 6.5 years) and increasing the risk of major bleeding (HR 1.50, 95% CI 1.33–1.69, NNH 210 for about 6.5 years; HR for gastrointestinal bleeding 1.52, 95% CI 1.34–1.73, NNH 334 for about 6.5 years), which is independent of baseline characteristics such as sex, age, and ulcer history. The reduction in ischemic stroke and transient ischemic attack produced by ASA (HR 0.80, 95% CI 0.71–0.89, NNT 623 for about 6.5 years) is offset by more hemorrhagic strokes (HR 1.32, 95% CI 1.12–1.55, NNH 927 for about 6.5 years), which carry a much worse prognosis.[22] We now have enough evidence to be confident that ASA does not reduce the risk of fatal myocardial infarction or overall mortality,[6,7] and patients interested in the potential of ASA to reduce cancer incidence or mortality will not find cause for optimism in the available evidence.[6,7,10,21]

However, for patients who are interested and able, their values and preferences should be respected in the choice of therapy. Several decision aids for primary prevention patients are available online, but only a minority include ASA as an option, and at present none are updated to include the full data set discussed here.[23] Speaking of preferences, a UK study about pill burden found that although some people would take a no-cost, no-toxicity pill every day for the rest of their lives even if it afforded no longevity benefit, 64% would require some extension of their lifespan in order to do so.[24] ASA offers neither lifespan extension nor freedom from toxic effects. Furthermore, for most patients still interested in ASA and considered to be at moderate or high cardiovascular risk on the basis of risk prediction models (e.g., Framingham, American Heart Association pooled cohort equations), ASA is probably the least effective of the risk-reduction strategies available (relative to statins, exercise, smoking cessation, blood pressure control) and carries the greatest magnitude of risk of a serious adverse drug reaction (major bleeding, intracranial hemorrhage) of any of these.[25] Hence, ASA should be the last intervention that patients contemplate for primary prevention, and only if they are deemed to have moderate or high risk after these modifiable factors have been thoroughly mitigated.

Given the large amount of high-quality data now available, it is possible but unlikely that longer-term trials (if ever conducted) and patient-level meta-analyses (which are sure to be) could reveal other truths about ASA, including subpopulations in which the benefit-harm ratio is meaningfully different one way or another. As of now, the most relevant question about ASA is the following: "Is there any group of primary prevention patients who clearly *are* good candidates for ASA?" One such group may be patients with or without diabetes who place very high value on an extremely small chance of avoiding a nonfatal coronary event (approximately 1 in 366 chance during about 6.5 years of taking ASA), are tolerant of the risk of major bleeding (approximately 1 in 210 chance during about 6.5 years of taking ASA; occurrence of about 1.7 major bleeds per nonfatal myocardial infarction prevented),[6,7] and ascribe no disutility to taking a pill daily that adds no longevity.

Clinicians and patients should continue to rely on much more effective and safe interventions than ASA, such as statins, smoking cessation, blood pressure control, and healthier lifestyles to reduce cardiovascular risk in primary prevention.

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2020 CSHP National Awards Program Winners
Programme national des prix 2020 de la SCPH : lauréats et lauréates

The winner of the **Hospital Pharmacy Student Award** (co-sponsored by the Canadian Society of Hospital Pharmacists [CSHP] and the Canadian Association of Pharmacy Students and Interns [CAPSI]) is **Dillon H Lee** (Edmonton, AB).

Excellence in Pharmacy Practice – Interprofessional Collaboration Award
Development of Standardized Opioid Prescriptions for Post-Laparoscopic Appendectomy and Cholecystectomy Surgeries and Implementation of Patient Information on Safer Opioid Use (completed at North York General Hospital, Toronto, ON)
Jenny C Chiu, Alice Watt

Excellence in Pharmacy Practice – Leadership Award
Sponsored by **Health*PRO* Procurement Services Inc.**
Development of a Patient-Centered Video Series to Improve Outcomes for Kidney and Lung Transplant Patients (completed at Saskatchewan Transplant Program, Saskatchewan Health Authority, Saskatoon, SK)
Holly Mansell, Nicola Rosaasen

Excellence in Pharmacy Practice – Patient Care Award
Sponsored by **Steri*Max* Inc.**
Radiology Exam and Postoperative/Post-Sedation Breastfeeding: Internal Initiatives and Information Documents (completed at CISSS de l'Outaouais, Gatineau Hospital, Gatineau, QC)
Nathalie Gagnon

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Development of Standardized Opioid Prescriptions for Post-Laparoscopic Appendectomy and Cholecystectomy Surgeries and Implementation of Patient Information on Safer Opioid Use

Excellence in Pharmacy Practice – Inteprofessional Collaboration Award

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Background: Opioid prescriptions with duration exceeding 7 days for acute pain were associated with double the likelihood of continued use 1 year later. Quantities prescribed vary widely between prescribers. Excess unused opioids are rarely disposed of properly. A 2017 Ontario Student Drug Use Survey showed that 11% of high school students reported non-medical use of opioids and 55% of the time they were obtained from home.

Objectives: The objectives were to standardize discharge opioid prescriptions focusing on laparoscopic appendectomy and cholecystectomy (LA & LC) surgeries and to develop a patient education sheet on opioids.

Methods: A baseline survey was conducted over 3 months in LA/LC patients to establish their opioid usage, pain control, and whether opioid education was received post-operatively. This data was used to develop a standardized prescription. A patient information sheet on proper opioid use, storage and disposal was developed in collaboration with ISMP Canada and support from the Canadian Patient Safety Institute. A post-implementation survey was completed to assess if patients had adequate supply of pain medications and pain control with the new standardized prescription, and to measure rates of opioid education.

Results: Pre-implementation, surgeons prescribed 20 to 30 opioid pills per prescription. The standardized prescription issued 10 tablets. This led to a 56% decrease in the number of opioids prescribed over the 3-months (from 2672 to 1182 tablets). Results showed that patients were satisfied with their pain control. Patient education on opioids increased from 8.6% to 44%

Conclusions: Implementing a standardized opioid prescription led to a decrease of 1490 opioid tablets prescribed over 3 months. This would amount to around 11,000 less opioid tablets prescribed over 1 year at 1 institution. The opportunity for other surgical programs and institutions to adopt this prescription would mean several thousand less opioids tablets available for diversion. Increasing patient education may potentially decrease opioid-related misuse.

Keywords: opioid, standard prescription, patient education, pain

Development of a Patient-Centered Video Series to Improve Outcomes for Kidney and Lung Transplant Patients

Excellence in Pharmacy Practice – Leadership Award Sponsored by HealthPRO Procurement Services Inc.

Mansell H[1], Rosaasen N[2], Mainra R[2,3], Shoker A[2,3], Hassan A[2,3], Trivedi P[4], Cardinal L[2], Fenton ME[2,5], Tam J[2,5]
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Background: Inadequate patient knowledge contributes to poor patient outcomes after transplantation. Kidney and lung transplant patients have indicated that the transplant process is confusing, and they want more education.

Objectives: 1) Conduct a needs assessment to determine optimal format and content, 2) develop a patient-centered educational intervention for kidney patients, 3) test the intervention's effectiveness, 4) develop a similar resource for lung transplant patients.

Methods: Three studies were undertaken providing qualitative and quantitative feedback from patients on the kidney waitlist, kidney transplant recipients, and health care providers working in transplantation. A video series was created for kidney patients by engaging patient-stakeholders, experts in medication adherence, video education, motivational psychology, and cultural education. Two randomized-controlled trials were designed to test the videos delivered electronically in pre- and post-transplant cohorts. Consultations with patients and caregivers from the lung association informed the content for lung transplant videos.

Results: 'Solid Organ Transplantation: An Educational Mini-Series for Patients' is a 6-part video series outlining the kidney transplant process in its entirety. The videos range between 3 and 24 minutes in length, are patient friendly in design, and incorporate animations to explain complex information to accommodate individuals with low health literacy. Patient testimonials align the content with principles of the adult learning theory. A similarly designed but newly scripted version of the series is intended for the lung transplant audience. Two multicenter, parallel arm, randomized controlled trials are currently being conducted to test the kidney videos (delivered electronically) in pre- and post-transplant cohorts, with collaborators from Saskatoon, Regina, Calgary, Edmonton, Halifax and Chicago.

Conclusion: These studies aim to determine whether electronic education can improve transplant knowledge, patient satisfaction and other patient outcomes (e.g. medication adherence). If proven beneficial, these interventions can be easily implemented and provide consistent, repeatable patient education at low cost, with little impact to existing health care personnel.

Keywords: transplant, video, electronic, education, patient-oriented research, patient perceptions

Radiology Exam and Postoperative/Post-Sedation Breastfeeding: Internal Initiatives and Information Documents

Excellence in Pharmacy Practice – Patient Care Award Sponsored by SteriMax Inc.

Gagnon N
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Background: During breastfeeding, tests and procedures requiring contrast media, anesthetics and analgesics may be prescribed. Too often, the tendency is still to tell women they have to pump and throw away their milk, even though this is rarely necessary. In addition, the information being provided is generally inconsistent between departments or healthcare professionals.

Objectives: Review the literature on drugs used in radiology, examination room or operating room in breastfeeding context. Develop a protocol or procedure. Provide written information.

Methods: An Internet search was conducted for such documents, but nothing was found. Phone calls to other CISSS, including those holding a "Baby Friendly Initiative" accreditation, were done; none of them had a protocol or procedure in place. Reference books, literature reviews and specialized databases were consulted.

Results: The use of these drugs in these contexts is a one-time event. They are rapidly eliminated from the plasma compartment, the amount likely to pass into the milk is generally very low with an unlikely digestive absorption in the infant. A resumption of breastfeeding is possible as soon as the patient is in a stable state and has regained a level of alertness authorizing her to stand up.

Conclusions: The procedure "Radiology exam in breastfeeding patient" has been in place since January 2017, while the medical protocol "Post-operative/post-sedation breastfeeding" has been in force since November 2018. The drugs involved are compatible with breastfeeding. The challenge is to widely disseminate these initiatives for the benefit of lactating patients and the children they breastfeed.

Keywords: breastfeeding, drug, contrast agent, radiology, sedation, postoperative

CSHP Professional Practice Conference 2020: Poster Abstracts / Conférence sur la pratique professionnelle 2020 de la SCPH : Résumés des affiches

Facilitated Poster Sessions: Discussions of original research and pharmacy practice projects

Séance animée de présentations par affiches : Discussions sur des projets de recherche originale et des projets dans le domaine de la pratique pharmaceutique

Sunday, February 2, 2020 • Dimanche 2 février 2020

Category: Infectious Diseases/Antimicrobial Stewardship

1. Antimicrobial Use Surveillance among Adult Inpatients at Hospitals Participating in a Canadian Sentinel Surveillance Program, 2009–2017
2. Trends in the Antimicrobial Resistance of *Serratia* Isolates Collected from Sunnybrook Health Sciences Centre Inpatients
3. Safety of Administering Cefazolin versus Other Antibiotics in Penicillin Allergic Patients with Anaphylaxis for Surgical Prophylaxis
4. Vancomycin Therapeutic Drug Monitoring in Adult Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Pneumonia: A Comparison of Trough Concentrations and Area Under the Concentration-Time Curve to Minimum Inhibitory Concentration
5. Evaluating Antimicrobial Use through Point Prevalence Surveys at a Canadian Children's Hospital
6. Resistance Patterns of *Acinetobacter* Isolates Collected over a 14-Year Period at Sunnybrook Health Sciences Centre

Category: Clinical Pharmacy Practice

1. Telepharmacist-Led Warfarin Program: A Prospective Observational Study in Rural and Remote Underserviced Communities
2. Pharmacy Clinical and Management Services: A Survey of Small Hospitals in Canada
3. Patients Support a Pharmacist-Led Best Possible Medication Discharge Plan (BPMDP) via Tele-robot in a Remote and Rural Community Hospital
4. Burnout in Hospital Pharmacists: An Ontario-Wide Survey
5. Evaluation of a Pharmacy Department Continuing Education Framework (EDGE)
6. Evaluating the Quality of Best Possible Medication Histories Performed by Pharmacy Technicians

Category: Pediatrics, Sleep, and Psychiatry

1. Drug Utilization Evaluation of Chlorothiazide in a Paediatric Quaternary Care Centre
2. Delirium in the Pediatric Intensive Care Unit: A Nested Case-Control Study
3. Exploration of Sleep Patterns, Sleep Hygiene and the Use of Sleep Aids among University Students
4. Evaluation of Cardiovascular Risk in Individuals with Serious Mental Illness
5. Impact of Pharmacist-Led Cognitive Behavioural Therapy for Insomnia: A Retrospective Chart Audit
6. The Effect of in Hospital Initiation of Long Acting Injection Antipsychotics on Time to Readmission

Category: Medication Decontamination, Pharmacy Administration, and Pharmacists in Research

1. Évaluation de l'efficacité de stratégies de décontamination pour cinq antinéoplasiques : irinotécan, méthotrexate, gemcitabine, 5-flurouracile et ifosfamide
2. Évaluation de l'acte pharmaceutique : une enquête auprès des chefs de départements de pharmacie du Québec
3. Évaluation d'une intervention à trois volets visant à accroître la visibilité de la présence et du rôle du pharmacien
4. Environmental Contamination with Nine Antineoplastic Drugs in 93 Canadian Centers
5. Environmental Scan of Hospital Pharmacist Participation in Research in Canada
6. Pharmacists' Experience, Motivation, Attitudes, Self-Perceived Competence and Training Needs to Conduct Pharmacist-Driven Research in a Tertiary Care Teaching Hospital

Monday, February 3, 2020 • Lundi 3 février 2020

Category: Drug Safety/Adverse Drug Events and Pharmacist Prescribing Activities

1. Disseminated Intravascular Coagulation and Autoimmune Hemolytic Anemia with Oxaliplatin Treatment for Metastatic Colon Adenocarcinoma: A Case Report
2. Impact of Ultrafiltration on Tobramycin Clearance and Dosing
3. Ceftaroline Monotherapy for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infective Endocarditis: Case Report
4. Description des activités réservées de la Loi 41 réalisées par les pharmaciens dans un hôpital universitaire
5. Terbinafine Induced Thrombotic Thrombocytopenic Purpura
6. Gemcitabine-Associated Atypical Hemolytic-Uremic Syndrome Treated with Eculizumab

Category: Drug Stability and Sterility

1. Stability of Morphine Solutions of 20mcg/mL, 40mcg/mL 100mcg/mL 200 mcg/mL, 1,000mcg/mL in Syringes Following Dilution with 0.9% Sodium Chloride at Room Temperature (25°C)
2. Stability of a New Generic Formulation of Bortezomib Injection (Apotex Brand) in Vials and Syringes Stored at 4°C and Room Temperature (25°C)
3. Stability of a New Generic Formulation of Bortezomib Injection (MDA Brand) in Vials and Syringes Stored at 4°C and Room Temperature (25°C)
4. Stability of 3.33 mg/mL Bicalutamide in Syringes and Amber Plastic Bottles Following Reconstitution with Sterile Water or Oral Mix Sugar Free at 4°C and Room Temperature (25°C)
5. Chemical Stability of Epinephrine Diluted in 0.9% Sodium Chloride and Stored in Polypropylene (PP) Syringes at 4°C and 25°C
6. Compatibility and Stability of Ketamine and Ringers Lactate at Room Temperature (25°C)

Category: Infectious Diseases/Antimicrobial Stewardship

1. Retrospective Review of Vancomycin Dosing for Non-Central Nervous System Infections in Patients Admitted to the Neonatal Intensive Care Unit
2. Trends in Antimicrobial Resistance for *Enterobacter* spp. Collected from Inpatients at a Major Canadian Tertiary Care Center: A Retrospective Analysis over 14 Years
3. Patterns of Antimicrobial Resistance among *Proteus* Isolates at Sunnybrook Health Sciences Centre: A 14-Year Retrospective Observational Study
4. Assessing the Use of a Standardized Allergy History Questionnaire in Patients with a Reported Penicillin Allergy
5. Implementation of Spectrum, an Antimicrobial Stewardship App at a Community Hospital
6. Trends in Antimicrobial Resistance of *Citrobacter* Isolates over a 14-Year Time Period

Category: Opioids and Clinical Pharmacy Practice

1. Evaluating the Efficacy and Safety of Buprenorphine Microdosing for Opioid Use Disorder: A Systematic Review
2. Wasting Better: An Interprofessional Evaluation of Narcotic and Controlled Drug Disposal Devices within a Pediatric Teaching Hospital
3. Pragmatic Observational Study of the Implementation of Narcotic and Controlled Drug Disposal Devices within a Pediatric Teaching Hospital
4. Opioid Prescribing at Discharge for General Surgery Patients: A Prospective Study
5. Opioid Use Post Discharge from Hip and Knee Arthroplasty
6. What Your Pharmacist Can Do for You: A Review of the Pharmacists' Role in an Allogeneic Hematopoietic Transplant Clinic

Tuesday, February 4, 2020 • Mardi 4 février 2020

Category: Clinical Pharmacy Practice

1. Development and Evaluation of a Diabetes Education Program for Pharmacists
2. A Drug Use Evaluation of Proton Pump Inhibitors at a Canadian Teaching Hospital
3. Systematic Deprescribing of Proton Pump Inhibitors: Pilot Study in a Geriatric-Medicine Unit at a Community Teaching Hospital
4. Documentation of Best Possible Medication History by Pharmacy Technicians in Ambulatory Care Clinics
5. The Comparison of Medication History Taken by Medical Team versus Pharmacy Team
6. Physical Assessment Educational Programs for Pharmacists and Pharmacy Students: A Systematic Review

Category: Medication Safety

1. Exploring Medication Safety Culture in New Brunswick Pharmacies Using the Medication Safety Culture Indicator Matrix
2. An Assessment of Safety Culture in Saskatchewan Pharmacy Practice
3. Medication Incidents Associated with Patients with Renal Impairment: A Multi-Incident Analysis
4. Lessons Learned from a Multi-Incident Analysis on Medication Incidents Associated with Patient Harm in Saskatchewan
5. Safety IQ: Lessons Learned from a Continuous Quality Improvement Program in Manitoba
6. Intravenous Medication Safety – A Quantitative Analysis of Medication Incidents

Category: Clinical Pharmacy Practice and Drug Stability and Sterility

1. Development, Dissemination and Evaluation of a "Direct Oral Anticoagulant Monitoring Tool" in Family Health Team Pharmacy Practice
2. Optimizing the Management of Heart Failure: Diuretic Therapy at Discharge
3. Roles and Perceptions of Pharmacists as Immunizers of Adult Patients in Tertiary Care Academic Hospitals: An Environmental Scan of Canadian Hospital Pharmacists
4. Development of Geriatric Pharmacology Infographics (GPI): An Internet Survey among Health Care Professionals
5. Closed System Transfer Device Sterility Testing to Validate Beyond-Use Date Extensions
6. Lipid-Based Formulation of a Vaccine Adjuvant Enhances Mucosal Immunity

Category: Quality Improvement and Key Performance Indicators

1. Clinical Pharmacy Key Performance Indicators and Pharmacist Job Satisfaction: A Mixed-Methods Study of Canadian Hospital Pharmacists
2. What Clinical Pharmacy Key Performance Indicators (cpKPI) Are Patients Receiving across Canada? A National cpKPI Patient Registry and Pooled Analysis
3. Implementation of Streamlined Electronic Workflow to Capture Key Performance Indicators (KPIs) for Pharmacists
4. Analysis of Pharmacist Clinical Documentation after CST Cerner Transformation
5. Missing Dose Message Audit Using a Closed-Loop Health Information System - A Pharmacy Quality Improvement Project
6. Discrepancies in "As Needed" Medications Prescribed during Hospitalization and at Discharge

The texts of poster abstracts are published exactly as submitted by the authors and have not undergone any copyediting by the Canadian Journal of Hospital Pharmacy. / *Le* Journal canadien de la pharmacie hospitalière *n'a pas soumis le texte des résumés des affiches à une révision linguistique et les publie ici tels que remis par les auteurs.*

Antimicrobial Use Surveillance among Adult Inpatients at Hospitals Participating in a Canadian Sentinel Surveillance Program, 2009–2017

Rudnick W[1], Science M[2], Thirion DJG[3,4], Abdesselam K[1], Choi KB[1], Pelude L[1], Amaratunga K[1,31], Comeau JL[5,6], Dalton B[7], Delport J[8], Dhami R[8,9,10], Embree J[11,12,13], Émond Y[14], Evans G[15], Frenette C[4], Fryters S[16], German G[17], Grant JM[18], Happe J[19], Katz K[20], Kibsey P[21], Kosar J[22], Langley JM[5,6], Lee BE[23,24], Lefebvre MA[4], Leis J[25], McGeer A[26,27,28], Neville HL[29], Simor A[27,30], Slayter K[5], Suh KN[31], Tse-Chang A[24], Weiss K[32], Conly J[7,33], and the Canadian Nosocomial Infection Surveillance Program
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Background: The association between antimicrobial use (AMU) and the emergence of antimicrobial resistance is well-documented. Our surveillance program conducts sentinel AMU surveillance at participating hospitals in Canada.

Objectives: Our surveillance program collates AMU from participating hospitals and establishes Canadian benchmarks.

Methods: Participating hospitals submit annual AMU data measured in defined daily doses (DDDs) per the World Health Organization Anatomical Therapeutic Chemical system. Surveillance includes systemic antibacterials (J01s), oral metronidazole (P01AB01), and oral vancomycin (A07AA09). Hospitals also submit patient-day (pd) denominators. Since 2014, hospitals have submitted data by ward-type.

Results: Between 2009 and 2017, 20–26 hospitals participated each year (31 participated ≥1 year; 12 in all years). During this period, overall AMU decreased from 645 to 589 DDD/1000pd (9%). Fluoroquinolones accounted for the majority of this decrease (126 to 72 DDD/1000pd, 43%). The top antimicrobials used in 2017 were cefazolin (88 DDD/1000pd), piperacillin-tazobactam (51 DDD/1000pd), and ceftriaxone (48 DDD/1000pd). Between 2009–11 and 2015–17, the antimicrobials with the largest absolute increases in use were amoxicillin-clavulanate (15 to 28 DDD/1000pd), ceftriaxone (31 to 43 DDD/1000pd), and cefazolin (65 to 76 DDD/1000pd). The antimicrobials with the largest relative increases were fosfomycin (0.0005 to 0.09 DDD/1000pd), daptomycin (1 to 3 DDD/1000pd), and doxycycline (5 to 15 DDD/1000pd). The antimicrobials with the largest absolute decreases in use were ciprofloxacin (74 to 43 DDD/1000pd), metronidazole (42 to 31 DDD/1000pd), and levofloxacin (33 to 24 DDD/1000pd). The antimicrobials with the largest relative decreases were gentamicin (6 to 2 DDD/1000pd), clindamycin (14 to 6 DDD/1000pd), and clarithromycin (7 to 3 DDD/1000pd).

Conclusions: Between 2009 and 2017, there was a 9% decrease in overall AMU at participating hospitals, a 43% decrease in fluoroquinolone use and more moderate increases in use of amoxicillin-clavulanate, ceftriaxone, and cefazolin. AMU surveillance is crucial for establishing Canadian benchmarks and informing stewardship targets.

Trends in the Antimicrobial Resistance of *Serratia* Isolates Collected from Sunnybrook Health Sciences Centre Inpatients

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Background: *Serratia* spp. are opportunistic environmental pathogens that cause a variety of nosocomial infections. These bacteria exhibit intrinsic resistance to many ß-lactam/ß-lactamase inhibitor combinations and early generation cephalosporins. Published data describing longitudinal trends for Serratia resistance rates are scarce. This novel study evaluated resistance patterns of *Serratia* isolates at a large Canadian tertiary care centre.

Objective: To identify changes in antimicrobial resistance patterns of *Serratia* clinical isolates collected at Sunnybrook Health Sciences Center (SHSC) between 2002–2016.

Methods: Susceptibility data for clinical isolates of *Serratia* collected from inpatients at SHSC Bayview campus between October 2002 and September 2016 were extracted from the SHSC Microbiology database. Linear regression was used to evaluate trends in ceftazidime, ceftriaxone, ciprofloxacin, co-trimoxazole, ertapenem, gentamicin, meropenem, piperacillin/tazobactam, and tobramycin resistance at a significance level of 0.05.

Results: A total of 1082 unique *Serratia* clinical isolates were identified. The majority of isolates were obtained from blood (20%), urine (24%), and respiratory (33%) samples. Most isolates were collected from patents admitted to Level 3 ICUs (43%) and greater than 48 hours after admission (72%). *S. marcescens* was the most prevalent species identified (95%); other species included *S.liquefaciens, S.odorifera, S.rubidaea, S.fonticola, S.plymuthica*, and undifferentiated *Serratia* spp. Nineteen percent of isolates exhibited resistance to a therapeutically active antibiotic agent, with 5% of isolates being multidrug resistant. Susceptibility to ceftazidime (~99%), ceftriaxone (~99%), ciprofloxacin (93%),

co-trimoxazole (~99%), ertapenem (~100%), gentamicin (99%), meropenem (~100%), piperacillin/tazobactam (~97%), and tobramycin (~92%) were stable across the 14-year study period.

Conclusion: SHSC *Serratia* clinical isolates exhibited low and stable resistance rates to all antimicrobials assessed over the 14 year study period, with only 5% having multidrug resistance. The continued low risk of antimicrobial resistance with *Serratia spp*. in a setting of an overall global rise in antimicrobial resistance provides some optimism in an otherwise bleak story.

Safety of Administering Cefazolin versus Other Antibiotics in Penicillin Allergic Patients with Anaphylaxis for Surgical Prophylaxis

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Background: Approximately 10% of patients report a history of penicillin allergy. Recent literature suggests cross-reactivity between cephalosporins and penicillins are due to side-chain similarities. Since cefazolin has a unique side-chain from other beta lactams, it can be safely administered in penicillin allergic patients for surgical prophylaxis. Since October 2018, our hospital updated all surgical prophylaxis pre-printed orders to use cefazolin in penicillin allergic patients, except in those with histories of cefazolin-specific allergy or delayed skin reactions (e.g. Stevens-Johnson syndrome).

Objectives: This study aims to retrospectively determine outcomes and safety of cefazolin as compared to other antibiotics for surgical prophylaxis in penicillin allergic patients with anaphylactic histories prior to implementation of cefazolin pre-printed orders.

Methods: All patients with reported anaphylactic reactions to penicillins prescribed surgical prophylaxis from October 9, 2017 to October 9, 2018 were included. Patients were stratified based on antibiotic received (i.e. cefazolin, clindamycin, vancomycin, other antibiotic) and a retrospective chart review was performed to assess for outcomes and safety.

Results: One-thousand-seventy-three prescriptions for prophylactic antibiotics were identified. Of these, 221 cases met inclusion with histories of anaphylaxis to pencillins: 77 (35%) cefazolin, 63 (28%) clindamycin, 33 (15%) vancomycin, and 48 (22%) other antibiotics. General and orthotrauma surgeries used the most cefazolin in penicillin allergic patients, while gynecology the most clindamycin and thoracics the most vancomycin. Amongst those receiving cefazolin, no critical incidents of allergic reactions were reported and the rates of adverse of events did not differ between any antibiotic group.

Conclusion: Cefazolin appears to be a safe option for surgical prophylaxis in patients with history of penicillin anaphylaxis. No differences in incidences of allergic reactions, complications or surgical delays were reported, as compared to alternate antibiotics. Further larger studies are needed to confirm our findings and determine rates of adverse events associated with the various antibiotic regimens.

Vancomycin Therapeutic Drug Monitoring in Adult Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia and Pneumonia: A Comparison of Trough Concentrations and Area Under the Concentration-Time Curve to Minimum Inhibitory Concentration

Marko R[1], Hajjar J[2], Nzeribe V[3], Pittman M[1], Deslandes V[2], Sant N[2], Cowan J[2], Patel R[2], Kyermentang K[2], Ramsay T[4], Zelenitsky S[5], Kanji S[1,4]
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Background: Vancomycin remains widely used for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, however treatment failure rates up to 50% have been reported. The correlation between vancomycin trough monitoring and efficacy outcomes continues to be controversial. Current evidence supports the use of the 24-hour area under the concentration-time curve to minimum inhibitory concentration (AUC_{24}/MIC) as the pharmacodynamic parameter most likely to predict outcomes in patients with MRSA-associated infections.

Objectives: To determine the discordance rate between trough levels and AUC_{24}/MIC values and how treatment failure and nephrotoxicity outcomes compare between those achieving or missing their pharmacodynamic targets.

Methods: Retrospective cohort study including hospitalized patients with either MRSA bacteremia or pneumonia treated with vancomycin. Trough concentrations were collected and extrapolated minimum concentrations (C_{min}) were calculated. AUC_{24}/MIC values were determined using validated population pharmacokinetic models. Discordance was defined as any instance where a patient's C_{min} corresponded to a C_{min} or AUC_{24}/MIC value falling outside the targets of 15-20 mg/L and 400-700, respectively. Predictors of treatment failure and nephrotoxicity were determined using logistic regression.

Results: 128 patients were included in the analyses. 57% of patients received an initial vancomycin dose < 15 mg/kg. The discordance rate between C_{min} and AUC_{24}/MIC values was 24%. Treatment failure and nephrotoxicity rates were 34% and 18%, respectively. No clinical variables were found to predict discordance. Logistic regression identified vancomycin starting after a positive culture result [OR 4.42 (95% CI 1.36–14.3)] and achieving a target AUC_{24}/MIC after 4 days [OR 3.48 (95% CI 1.39–8.70)] as modifiable predictors of treatment failure.

Conclusions: The relationship between vancomycin monitoring and outcomes is likely confounded by inadequate empiric/initial dosing. Before modifying practice with respect to vancomycin monitoring, focus should be shifted towards optimizing appropriate antibiotic selection and both empiric and weight-based dosing.

Evaluating Antimicrobial Use through Point Prevalence Surveys at a Canadian Children's Hospital

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Background: Establishing an Antimicrobial Stewardship Program (ASP) that includes improving and measuring appropriate antimicrobial use is an Accreditation Canada requirement. Our hospital participated in a Point Prevalence Surveys (PPS) to compare antibiotic use across Canada and evaluate the impact of ASP interventions locally. Current ASP interventions include: prolonged use of broad-spectrum antibiotics, surgical prophylaxis, and beta-lactam allergy (BLA) de-labeling.

Objective(s): To identify the prevalence of patients on empiric broad spectrum antimicrobial therapy (≥4 days), post-operative surgical prophylaxis, and patients reporting a BLA in order to evaluate ASP initiatives.

Methods: Two 1-day, PPS were completed in the Fall (November 2018) and Winter (February 2019) at a tertiary-care pediatric hospital as a part of a larger cross-sectional study which compared antibiotic use over time between 15 Canadian pediatric hospitals.

Results: A total of 576 patients were captured during the PPS with 291 in the Fall and 285 in the Winter. The PPS identified that 252 (44%) patients were taking at least one antimicrobial, which accounted for 462 antimicrobial prescriptions. The majority were intravenous (66%); 23% were enteral, and 11% were topical or inhaled. Six (1.2%) prescriptions beyond day 3 were empiric vancomycin or meropenem. Systemic antibiotics were given more than 24 hours post-operatively as prophylaxis to 13 (6.4%) of 202 eligible patients. Seventeen patients (3%) had documented beta-lactam allergies.

Conclusion(s): Prolonged use of broad spectrum empiric antibiotics and post-operative antibiotics were higher in the fall than winter, but overall rates are low. BLA were present at a rate consistent with previous studies. Current ASP interventions are effective, but continued efforts are necessary to improve and measure the impact.

For the table that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Resistance Patterns of *Acinetobacter* Isolates Collected over a 14-Year Period at Sunnybrook Health Sciences Centre

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Background: *Acinetobacter*'s propensity for multidrug resistance makes it a challenging nosocomial pathogen to treat. Surveillance data from the United States and Europe suggest that *Acinetobacter* bacterial infections carry a crude mortality risk of 30 – 75%, in part as a consequence of inappropriate antibiotic selection; however, data describing patterns of antimicrobial resistance for *Acinetobacter* isolates in Canada are lacking.

Objective: To identify changes in antimicrobial resistance for *Acinetobacter* spp. clinical isolates collected at Sunnybrook Health Sciences Center (SHSC) between 2002 – 2016.

Methods: Susceptibility data for *Acinetobacter* clinical isolates collected from SHSC inpatients between October 2002 to September 2016 were retrospectively extracted from the SHSC Microbiology database. Annual trends in ceftazidime, ceftriaxone, ciprofloxacin, co-trimoxazole, gentamicin, meropenem, piperacillin/tazobactam, and tobramycin resistance rates were analyzed using linear regression with a significance level of 0.05.

Results: Of the 544 *Acinetobacter* isolates identified, 282 (52%) were collected from patients admitted to Level 3 ICUs. Thirty-three percent were collected from respiratory sources, 23% from urine, 19% from blood, and 24% from other sources. Seventeen percent of isolates were multidrug resistant, 7% of isolates were extensively-drug resistant, and one isolate exhibited pan-drug resistance. Resistance of *Acinetobacter* isolates to piperacillin/tazobactam and meropenem increased over time (+2.0% resistant/year, p=0.009; and +1.3% resistant/year, p=0.142, respectively). Conversely, resistance to ciprofloxacin decreased over the study period (-1.4% resistant/year, p=0.086). Resistance rates for ceftazidime, ceftriaxone, co-trimoxazole, gentamicin, and tobramycin remained relatively stable across the 14-year study period.

Conclusion: This study adds to the existing body of literature on *Acinetobacter* resistance and is the first to evaluate trends in the susceptibility of this opportunistic pathogen over an extended period of time in Canada. Given that *Acinetobacter* commonly exhibits multidrug resistance, knowledge of Canadian resistance trends provides valuable guidance in the selection of appropriate empiric antimicrobial agents to treat these infections.

Telepharmacist-Led Warfarin Program: A Prospective Observational Study in Rural and Remote Underserviced Communities

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Background: Warfarin is a high risk medication prescribed to treat and prevent clotting disorders. Monitoring with a blood test ensures safe and effective therapy; if not kept within a narrow range, puts patients at increased risk of harm due to clotting or bleeding. Monitoring, prescribing and follow-up is complex requiring close integration between the patient, pharmacist, lab and physician. Times required to conduct a pharmacist-led warfarin program remotely (dosing, monitoring, patient education and follow-up) are unknown.

Objectives: To describe pharmacist task time requirements in relation to patient encounters, and proportions, administrative and clinical tasks, to conduct a warfarin program.

Methods: This prospective observational cohort study included patients enrolled in the pharmacist warfarin program in 6 remote communities and 1 Family Health Team (FHT) for 11 days over a 3-week period. Pharmacists documented the following time requirements per patient encounter: program software entry (assessment/documentation, dosing, monitoring, patient letter), calls to physician/local health care facility/patients, fax/email/entry into electronic medical record and administrative duties (reports, reminders, faxing prescriptions, program maintenance). Categorical and continuous data described using descriptive statistics and tests for association.

Results: Pharmacists reported 125 patient encounters, with a mean time of 14 minutes per encounter. Documentation of administrative activities occurred 79 times, with a mean duration of 11 minutes. Direct patient care accounted for 60% of program time compared to 40% for administrative duties. FHT represented 33% of program encounters. Mean times to dose/enter in software, gathering patient information, documentation/ letter, calling patient and administrative activities were 3.26, 3.08, 5.07, 2.97, 12.98 minutes respectively.

Conclusions: Data on pharmacist tasks in relation to patient encounters, time requirements and task proportions, both administrative and clinical, to conduct a warfarin program remotely enables both telepharmacy providers and healthcare leadership to make informed decisions on human resources required to conduct a pharmacist-led warfarin program.

Pharmacy Clinical and Management Services: A Survey of Small Hospitals in Canada

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Background: The CSHP Hospital Pharmacy in Canada Report 2016/17 representing180 pharmacy departments across Canada provides quantitative data on pharmacy services clinical and management information in relation to hospital size, type and geographic region for pharmacy and hospital administrators to use in identifying baseline, benchmarking current, and planning enhanced pharmacy services. Unfortunately, for over 300 small hospitals in Canada, this quantitative data remains unknown; hospitals with less than 50 beds remain unrepresented and uninformed.

Objectives: Primary: To collect information and analyze data from small hospitals pharmacy clinical and management services.

Methods: In April 2019, emails to pharmacy administrators of hospitals with less than 50 beds requesting survey participation were sent including the CSHP Hospital in Canada Report and copy of the questionnaire/ link to the survey website. The surveyor followed up with potential respondents and provided reminders and support with survey completion. Study deadline was 30/07/19. Data was downloaded, and results tabulated by the research analyst who prepared summary tables for all the variables captured by the survey.

Results: Twenty-seven eligible hospitals were invited with an 89% completion rate representing 3 provinces and 6 Ontario Local Health Integration Networks. Median hospital size was 19 acute beds (range 0-40), and 4 (range 1-12) programs. Most pharmacies (63%) implement the clinical generalist practice model with limited differentiation of roles. Over half the hospitals reported that pharmacists documented medication reconciliation on admission and 45% on discharge in 76-100% of patients. Data on clinical pharmacy activities and performance, clinical pharmacy key performance indicators, pharmacy department composition, evaluation of clinical services, drug distribution, operation hours, medication administration records and compliance standards were also analyzed.

Conclusions: Data collected from small hospitals provides useful pharmacy clinical and management information to inform hospital administration and pharmacy leaders currently unable to share information on clinical and administrative practices within their institutions.

Patients Support a Pharmacist-Led Best Possible Medication Discharge Plan (BPMDP) via Tele-robot in a Remote and Rural Community Hospital

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Background: Medication reconciliation reduces the risk of preventable medication-related adverse events (ADE); pharmacists have demonstrated they are invaluable in the process. A BPMDP is an accurate list of medications a patient will take when discharged from hospital; home medications stopped, changed and new medications. Despite a publicly funded universal healthcare system, there is inequity in healthcare access; many hospital on-site pharmacists are non-existent. To our knowledge, there are no studies on the extension of a visual presence via a mobile robotic platform with real-time audiovisual communication by pharmacists.

Objectives: Primary: To explore how patients perceive a pharmacist-led real-time BPMDP utilizing a telerobot. Secondary: Describe BPMDP time requirements, unintentional medication discrepancies (MD) and program inefficiencies/barriers and facilitators.

Methods: This prospective cohort pilot study enrolled adult patients admitted to a small community hospital Sept/2017-Feb/2019 who were at high risk of ADE with an anticipated length of stay of 72 hours or greater. Pharmacists created BPMDPs, identified MDs, resolved drug therapy problems (DTP), and interviewed/counselled patients using real-time mobile robotic technology. Thereafter, patients completed an anonymous satisfaction questionnaire. Prescriber discharge MDs (classified by class, type, cause, and intervention), and interview inefficiencies/barriers and facilitators were collected.

Results: Nine patients completed an interview, with a median of 11 medications/patient. Interview agreement rate was 75%, 100% of patients felt comfortable with the robot, and 76% felt care was better. MD rate was 78%, most-frequent MD type, medication omission (71%), class, cardiovascular medication (43%), cause, the medical system (88%), reason, an inaccurate admission medication history (BPMH). Median times for interview preparation, interview, and MD/DTP resolution were 45, 15, and 10 minutes respectively.

Conclusions: Using a telerobot to provide pharmacist-led BPMDPs is acceptable to patients and an innovative, effective solution to identify/ resolve MDs, and support patients and their providers in hospitals that lack in-person access to pharmacists.

Burnout in Hospital Pharmacists: An Ontario-Wide Survey

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Background: Clinician burnout is a work-related syndrome characterized by feelings of emotional exhaustion, depersonalization and reduced personal accomplishment. It is associated with reduced quality of care, medical errors and mental illness. Although extensively studied in Canadian physicians and nurses, there is no previous research to our knowledge assessing burnout in Canadian pharmacists.

Objectives: To determine the prevalence of burnout and its associated risk factors among Ontario hospital pharmacists and explore the current status and interest for preventative programs in undergraduate pharmacy curricula.

Methods: A cross-sectional online survey was conducted of hospital pharmacists recruited through the Canadian Society of Hospital Pharmacists (CSHP) Ontario Branch and hospital e-mail distribution lists. Respondents completed the Maslach Burnout Inventory (MBI) and questions on personal and career characteristics and professional satisfaction. A multivariate regression analysis was used to determine factors independently associated with burnout. All Canadian pharmacy schools were surveyed about their burnout curricula in a separate online questionnaire.

Results: Of 2465 hospital pharmacists in Ontario, 270 responded (11% response rate). The majority of respondents were females (77%) working full-time (90%) in the acute care setting (39%). The burnout rate was 61.1% (95% confidence interval 55.5% to 66.8%). Factors found to be independently associated with burnout were dissatisfaction with work-life balance (OR 2.62, p=0.005) and feeling that contributions were unappreciated (OR 2.60, p=0.019). Of those burned out, based on the

MBI, 23% were not self-aware. Nine of the 10 Canadian pharmacy schools do not currently have burnout prevention curricula; 8 would be interested in incorporating such programs.

Conclusions: The rate of burnout among Ontario hospital pharmacists is high and preventative action is needed. Opportunities to improve pharmacist resiliency and reduce institutional stressors exist at both undergraduate and postgraduate levels.

Evaluation of a Pharmacy Department Continuing Education Framework (EDGE)

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Background: Provision of quality, professional education is complex. Modern and interactive educational practices improve effectiveness of adult learning. Competence in the successful delivery of continuing education may be facilitated with a standardized framework.

Objectives: Develop and pilot a continuing education framework for clinical pharmacists in Saskatchewan Health Authority (SHA) Regina; evaluate learning objectives for alignment with SHA Clinical Practice Standards; evaluate impact of a framework on knowledge transfer and retention in pharmacists with varying experience; and evaluate pharmacist satisfaction with the education framework, as both learners and facilitators.

Methods: This prospective pilot project included development, implementation, and evaluation of an education framework for provision of pharmacist-led education sessions. Development was informed by literature regarding adult learning principles, MainPro+®, CCCEP® Accreditation Standards, and focus group feedback. Pre- and post-session questionnaires based on session-specific learning objectives were completed to determine level of knowledge transfer, and repeated 2 weeks post-session to determine level of knowledge retention. Pre- and post-intervention satisfaction surveys were distributed.

Results: Of 53 eligible pharmacists, 27 (50%) consented to participate. Four education sessions were completed utilizing the framework and 19 participants completed both pre- and post-session questionnaires; the mean knowledge score increased from 57.7% to 84.1% ($p<0.01$), indicating successful knowledge transfer. Of these 19, 16 participants completed both post-session and retention questionnaires with no significant change in mean knowledge score (86.4% to 86.7%, $p=0.96$), suggesting knowledge was maintained 2 weeks post-session. Twenty-six and 17 pharmacists completed the pre-and post-intervention satisfaction surveys respectively. With use of the framework learner satisfaction significantly improved, facilitator confidence increased, and 94% (16/17) agreed that session learning objectives aligned with SHA Regina Clinical Practice Standards.

Conclusion: Implementation of a continuing education framework based on best practices in adult education achieved knowledge transfer and retention, and improved facilitator and learner satisfaction with continuing education.

Evaluating the Quality of Best Possible Medication Histories Performed by Pharmacy Technicians

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Background: Majority of patients admitted into hospitals are classified as having highly preventable adverse drug events (ADEs) causing temporary/permanent disability and extending hospitalization time. Medication reconciliation (MedRec) is known to be a crucial process in preventing ADEs.

Description: Pharmacy technicians have been performing best possible medication history (BPMH) for directly admitted and soon-to-be-admitted patients. In April 2018, a new electronic health record was implemented, and BPMH documentation switched from paper to electronic.

Action: A random, convenient 3-month sample of BPMHs performed between 21Apr-21Jul 2019 were reviewed. Discordance was calculated using deLemos et al method. Inclusion: Patients 18 years and older with prescribed medications, over-the-counter acetylsalicylic acid and non-steroid anti-inflammatory because of the clinically significant roles they have in patients.

Evaluation: MedRec consists of 3 phases: collection, verification and reconciliation. BPMH encompass the first 2 phases. In the paper world, verification was represented by the verification column. In the electronic world, verification is recorded by compliance status. Verification is key to a quality BPMH. Discordance relies on the assumption that patients do not always take medications as dispensed, and a BPMH is likely to detect these differences. We use this as a marker of quality: the more differences, the higher discordance = higher quality BPMH.

$$\frac{\text{number of discordant medications}}{\text{total medications listed in provincial dispensing database and ultimately ordered in hospital}}$$

For the table that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Pharmacy technicians performed the highest quality BPMHs and their quality was similar for paper and electronic documentation.

Implications: Pharmacy technicians gather excellent histories that allow physicians and pharmacist to assess appropriateness and provide continuity of care.

Drug Utilization Evaluation of Chlorothiazide in a Paediatric Quaternary Care Centre

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Background: Chlorothiazide (CTZ), the only intravenous thiazide diuretic available in Canada, has been used at the Hospital for Sick Children since 2011. Prescribing restrictions were implemented due to limited published paediatric evidence and high cost.

Objectives: The primary objectives were to evaluate CTZ usage, cost, and adherence to formulary guidelines.

Methods: This was a single-center, retrospective observational study. Included patients received at least one dose of CTZ between June 2, 2018, and May 31, 2019. Data was collected for dose, duration,

indication, and costs. Usage was considered adherent if other diuretics were optimized. Costs were assessed from all CTZ orders while adherence was assessed from initial orders. Data was analyzed using descriptive statistics.

Results: A total of 181 CTZ orders (with 92 initial orders) were included for 74 patients. CTZ was prescribed in either post-op cardiac patients (59%) or medical (non-post-op cardiac) patients (41%). Adherence to formulary dosing (5 mg/kg/dose q6-12h) was 84.8% with a median (range) duration of 3.5 (1-37) days per course. Non-adherence to guidelines was 64.2% overall. Non-adherence to enteral thiazide criteria was attributed to lack of use (67.4%) or not optimizing enteral thiazide dose (32.6%). Non-adherence to IV loop diuretic criteria was attributed to not optimizing IV loop dose in all cases. The total CTZ cost during the study period was $134,000. The costs of non-adherent initial orders ($43,500) contributed to 68% of the total costs of initial orders ($64,000).

Conclusion: Results indicate that there is room for improvement in maximizing enteral thiazide and IV loop diuretic use and reducing duration of CTZ use. Future studies on de-prescribing and resultant cost savings with improved adherence and optimization of diuretics are needed.

Delirium in the Pediatric Intensive Care Unit: A Nested Case-Control Study

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Background: Delirium is a concerning neurologic dysfunction due to an underlying illness or its treatment.

Objectives: To determine the incidence of delirium and characterize its risk factors and consequences in critically ill children at our pediatric intensive care unit (PICU).

Methods: Retrospective nested case-control study enrolling all children admitted to our PICU for ≥12 hours between September 1, 2017 and August 31, 2018. For each delirious child (Cornell Assessment of Pediatric Delirium score ≥9), we selected an age-matched control.

Results: Forty-four (7%) of the 655 children admitted were screened for delirium. Thirty-nine (89%) of them screened positive, yielding a 6% delirium incidence. Most children (72%) with delirium were ≤5 years old. The median (IQR) onset of delirium was PICU day 7 (4,8), and median (IQR) duration of delirium was 3 (2,5) days. Nine (23%) children received antipsychotic treatment. The severity of illness was not statistically significant different between the case and control groups. Children with delirium were exposed to higher total doses of opioids (median 5 vs 0 mg/kg morphine equivalents), benzodiazepines (median 8 vs 0 mg/kg midazolam equivalents), and dexmedetomidine (median 0 mg/kg in both groups) ($p<0.001$ for all comparisons). The duration of exposure was also longer for opioids (median 5 vs 2 days, $p<0.001$), benzodiazepines (median 8 vs 0 days, $p=0.02$), dexmedetomidine (median 2 vs 0 days, $p<0.001$). Children with delirium had a longer PICU length of stay (median 10 vs 3 days, $p<0.001$), duration of mechanical ventilation (median 6 vs 2 days, $p<0.001$), and more withdrawal (69% vs 8%, $p<0.001$).

Conclusions: The incidence of delirium is 6%, but only a minority of children were screened for delirium. Our PICU has recently increased delirium screening to include more children. Further opportunities to optimize screening and management practices in pediatric delirium should be explored.

Exploration of Sleep Patterns, Sleep Hygiene and the Use of Sleep Aids among University Students

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Background: Sleep is an important component of healthy lifestyles. Worldwide reports suggest that one in every three adults suffers from insomnia. University students are vulnerable to insomnia due to their stressful lifestyle and inconsistent sleeping schedules which contribute to poor sleep hygiene.

Objectives: The purpose of this study is to explore the prevalence of sleeping problems among university students in and to investigate factors contributing to insomnia development.

Methods: A cross-sectional survey utilizing the Pittsburgh Sleep Quality Index (PSQI) and the Sleep Hygiene Index (SHI) questionnaires were administered to a sample of university students in either English or Arabic. An online survey, built using Survey Monkey software, was sent to all the sample university students through e-mail. Descriptive and inferential statistics were used to analyse and report the findings.

Results: A total of 2,062 students responded to this survey. Most of the respondents were females (85%) in their late teens or early twenties (70%). Most respondents were from the colleges of Arts and Sciences, Business and Economics and Engineering (33.3%, 19.3% and 15.7%, respectively). Around 25% of the participating students reported using sleep aids and 15.6% of them used sleep aids within the past month. The PSQI score revealed that around 69.7% of the participants have poor sleep quality (PSQI score >5) and 64% experienced excessive daytime sleepiness. SHI scores for 65.7% of the students were between 14 and 26, indicative of poor sleep hygiene. Also, there was a positive association between the global PSQI score and the SHI scores with a correlation coefficient of 0.391 ($p < 0.0001$).

Conclusion: The findings of this study suggest that poor sleep quality and inadequate sleep hygiene practices are common among this sample of university students, both of which may have a negative impact on students' academic performance, findings that warrants further investigation.

Evaluation of Cardiovascular Risk in Individuals with Serious Mental Illness

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Background: Individuals with serious mental illness (SMI) experience premature death, likely as a result of increased rates of metabolic disorders and major cardiovascular events. Strong evidence indicates that the risk of developing cardiovascular disease (CVD) is higher in people with SMI. Several studies point to inequities in assessing and managing CVD risk in people who experience SMI.

Objectives: The purpose of this study was to estimate the risk for developing CVD in a sample of individuals with SMI attending an outpatient mental health clinic.

Methods: CVD risk was estimated using the World Health Organization/ International Society of Hypertension (WH0/ISH) risk prediction charts for Eastern Mediterranean regions (including Qatar). For those patients with a recorded total cholesterol and high-density-lipoprotein cholesterol (HDL) level, the calculator from the American Heart

Association and the American College of Cardiology (AHA/ACC) was also used. Height and weight were obtained to determine the body mass index (BMI). Data analysis was carried out through SPSS® software.

Results: Of 346 SMI patients included in the cohort, 28% (n=97) had obtainable data to estimate their CVD risk using the AHA/ACC calculator and 32.7% (n=113) using the WHO/ISH CVD risk tables. The cohort had a mean probability of developing CVD or have a major cardiovascular event in the next 10 years of 7.47%, of whom 33% (n=32) were at high risk (AHA/ACC ≥7.5%). When using the WHO/ISH CVD risk tables, significantly lower proportion of patients were estimated to be at high risk (≥20%) and 7.1% (n=8) at moderate risk (10-20%). There was no significant difference in CVD risk among individuals with BMI higher or lower than 30 (p=0.815).

Conclusion: There is high prevalence of CVD risk factors among people with SMI. Adherence to monitoring guidelines and proper documentation of CVD risk in this population is needed.

Impact of Pharmacist-Led Cognitive Behavioural Therapy for Insomnia: A Retrospective Chart Audit

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Background: Cognitive behavioural therapy for insomnia (CBTi) is a first line treatment for insomnia. Several systematic reviews exist describing the significant benefits of CBTi, mostly provided by nurses or psychologists. Unfortunately, wait lists to receive CBTi are long and in some regions the service is not available. Evidence for pharmacists assisting patients with insomnia is minimal. Only one previous study has evaluated pharmacist-led behavioral therapies for insomnia, but it did not include any cognitive interventions.

Objective: The objective of this study was to measure the impact of CBTi, administered by pharmacists, in an ambulatory outpatient clinic setting.

Methods: This study was a retrospective chart audit. Patients were included if they were referred for and completed a CBTi intervention from the pharmacist at one of two outpatient ambulatory care clinics in Saskatoon, Saskatchewan (Canada). Sleep log parameters and insomnia severity index scores were compared at baseline and post CBTi. In addition, data on discontinuation of hypnotic medications were analyzed.

Results: A total of 183 patients were referred for CBTi and 78 completed the intervention. Improvements were observed in the following sleep parameters pre vs. post CBTi: insomnia severity index (18.2 vs. 7.9, p<0.001), sleep onset latency (47.9 minutes vs. 28.0 minutes, p<0.001), wake after sleep onset (60.7 minutes vs. 36.2 minutes, p<0.001), number of awakenings (2.0 vs 1.7, p=0.003), and sleep efficiency (78.2% vs. 86.1%, p<0.001). The proportion of patients using hypnotics was reduced from 71.8% to 52.6% (p<0.001).

Conclusions: This study suggests there is value in CBTi provided by pharmacists in ambulatory clinics. Improvements in sleep indices were both statistically and clinically significant (i.e., insomnia severity index score reduction of ≥ 7 points is considered clinically significant). Randomized trials are needed to confirm the benefit of CBTi when delivered by pharmacists in a variety of practice settings.

The Effect of in Hospital Initiation of Long Acting Injection Antipsychotics on Time to Readmission

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Background: High rates of oral antipsychotic nonadherence in schizophrenia is associated with increased hospitalization risk, relapse, emergency care use, and decreased quality of life. Long acting Injections (LAI) are used to improve adherence. In a meta-analysis of mirror-image studies, LAIs were superior in preventing hospitalizations. We examined the effect of inpatient initiation of LAIs on time to readmission.

Objectives: We compared the time to first readmission after initiation of a LAI antipsychotic, to the time since the last admission while on an oral antipsychotic. The secondary objectives were to determine the effect on mean time between all readmissions, mean total days in hospital and prescribing patterns of LAIs.

Methods: This was a retrospective mirror-image study of patients receiving LAI antipsychotics for the first time from January 1 - December 31, 2015. Data was collected for two years before and after the index admission. The primary outcome was analyzed by Kaplan-Meier plot and log-rank test. Secondary outcomes were analyzed by paired t-tests.

Results: For the primary outcome, mean times to first readmission were 436.5 days and 576.5 days while patients were on oral antipsychotics and LAI antipsychotics, respectively. However, log-rank test of these Kaplan-Meier curves showed no statistically significant difference in the proportion of patients without readmission (Mantel Cox χ^2=3.288, P=0.070). The difference in mean time between all readmissions was 96.9 days (95%CI -8.3-202.1 [P = 0.070]). The difference between the total days in hospital was 10.9 days (95% CI -23.2-1.3 [P = 0.079]). Of the patients initiated on a LAI, 16% had no oral antipsychotic therapy prior to the index admission. LAI antipsychotics were primarily prescribed for schizophrenia.

Conclusion: The results suggest that hospital initiation of LAI antipsychotics could result in longer times to readmission and a decrease in total days in hospital, however statistical significance was not reached.

Évaluation de l'efficacité de stratégies de décontamination pour cinq antinéoplasiques : irinotécan, méthotrexate, gemcitabine, 5-flurouracile et ifosfamide

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Contexte: Des traces d'antinéoplasiques sont présentes sur les surfaces même après nettoyage. Des travaux préliminaires ont permis de déterminer la stratégie à prioriser dans l'entretien des surfaces post-contamination au cyclophosphamide.

Objectifs: Tester une stratégie d'entretien des surfaces post-contamination volontaire par cinq antinéoplasiques : irinotécan, méthotrexate, gemcitabine, 5-fluorouracile et ifosfamide.

Méthodologie: Étude descriptive. Réalisée dans une salle avec une hotte (classe IIB2). Une zone de 600 cm^2 en acier inoxydable du plancher de la hotte a été contaminée concurremment avec 1 ug d'irinotécan (I),

1 ug de méthotrexate (M), 5ug de gemcitabine (G), 10ug de 5-fluorouracile (5FU) et 15 ug d'ifosfamide (IF). Nous avons testé l'efficacité d'une décontamination avec quatre lavages successifs avec ammonium quaternaire; nous avons répété la simulation avec quatre lavages successifs avec hypochlorite de sodium (NACl0) 0,1%. Une dernière simulation avec un lavage avec eau a été également réalisée. Tous les tests ont été faits en triplicata. Les limites de détection étaient respectivement de 0,003ng/cm^2, 0,002ng/cm^2, 0,004ng/cm^2, 0,001ng/cm^2 et de 0,004ng/cm^2.

Résultats: 36 prélèvements ont été réalisés. L'efficacité d'un lavage (eau) variait de 99,5% (M) à 99,79% (IF); l'efficacité d'un lavage (ammonium quaternaire) variait de 99,48% (IF) à 100% (5FU); l'efficacité d'un lavage (NACl0) variait de 99,62% (IF) à 100% (I, M, G, 5FU). L'efficacité d'un 2ème lavage (ammonium quaternaire) était respectivement de 99,82% (M), 99,97% (GEM) et 100% pour les autres. Il faut un quatrième lavage pour éliminer G et des traces persistent encore de M. L'efficacité d'un 2ème lavage (NACl0) variait de 99,96% (G) à 100% (I, IF, M, 5FU).

Conclusion: Il est possible de décontaminer les surfaces contaminées avec irinotécan, méthotrexate, gemcitabine, 5-fluorouracile et ifosfamide avec un ammonium quaternaire, de l'hypochlorite de sodium et de l'eau. Toutefois, plus d'un nettoyage peut être nécessaire pour éliminer toute trace détectable.

Évaluation de l'acte pharmaceutique : une enquête auprès des chefs de départements de pharmacie du Québec

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Contexte: Afin d'assurer une prestation sécuritaire des services et soins pharmaceutiques et pour répondre aux exigences du Code de déontologie des pharmaciens, il est nécessaire d'évaluer la pratique pharmaceutique.

Objectif: Décrire les pratiques entourant l'évaluation de l'acte pharmaceutique en établissement de santé au Québec.

Méthodologie : Étude descriptive transversale auprès de tous les chefs de départements de pharmacie du Québec. Questionnaire en ligne comportant 23 variables. Une échelle de Likert à quatre choix (TA=très en accord, PA=partiellement en accord, PD= partiellement en désaccord, TD=totalement en désaccord) a été utilisée pour les variables de perception. Le questionnaire en ligne (SurveyMonkey, Palo Alto, CA, ÉUA) a été prétesté et partagé par courriel du 23 au 30-3-2019. Un seul rappel a été expédié par courriel. Seules des statistiques descriptives ont été effectuées.

Résultats: Vingt-cinq chefs de département ont répondu à l'enquête (taux de participation de 83%). L'enquête révèle la présence d'un comité d'évaluation de l'acte pharmaceutique dans 40% (10/25) des départements de pharmacie. Les méthodes d'évaluation par rapportées par les répondants comprennent la tenue de revue par critères explicites (89%, 8/9), l'évaluation d'indicateurs (56%, 5/9) la revue de dossiers patients spécifiques (33%, 3/9) et critères implicites (33%, 3/9). Parmi les centres n'ayant pas encore de comité d'évaluation de l'acte pharmaceutique, neuf envisagent la mise en place d'un tel comité d'ici 24 mois.

Conclusions: Les chefs de départements de pharmacie déclarent la présence d'un comité d'évaluation de l'acte pharmaceutique dans 10 départements de pharmacie au Québec. De plus, neuf répondants prévoient la mise en place d'un tel comité dans les 24 prochains mois. L'enquête met également en évidence les pratiques et perceptions des chefs de départements de pharmacie en ce qui concerne l'acte pharmaceutique. Il n'existe pas de consensus quant aux comités appropriés de discussion pour des événements en lien avec la pratique pharmaceutique.

Évaluation d'une intervention à trois volets visant à accroître la visibilité de la présence et du rôle du pharmacien

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Contexte: On retrouve des pharmaciens dans la plupart des programmes de soins hospitaliers à l'échelle du Canada. Toutefois, on dispose de peu de données sur la visibilité associée à cette présence.

Objectifs : Décrire et évaluer la faisabilité d'implanter une intervention à trois volets visant à accroître la visibilité du pharmacien et de son rôle dans l'équipe traitante, pour permettre d'optimiser les soins pharmaceutiques. Comparer la perception et la satisfaction des parents et des soignants exposés à des soins pharmaceutiques usuels et des soins pharmaceutiques intégrant l'intervention.

Méthodologie : Étude expérimentale randomisée-contrôlée à simple aveugle au CHU Sainte-Justine chez des patients admis dans les unités de pédiatrie entre le 5-3-2019 et le 8-8-2019. Les soins pharmaceutiques usuels incluent: revue quotidienne de dossier, participation à la tournée médicale, rencontre avec les patients et intervention si requis. En sus des soins usuels, l'intervention inclut: remise d'une brochure d'information sur les services et soins pharmaceutiques, accès à une ligne téléphonique d'assistance et complétion par le pharmacien d'un formulaire de congé standardisé.

Résultats : 641 participants ont été inclus dans l'étude (321 intervention c. 320 témoin). La brochure a été remise à tous les parents du groupe intervention. Douze appels téléphoniques ont été placés via la ligne téléphonique d'assistance. Le formulaire de congé standardisé a été complété pour 46,7% (150/321) des participants du groupe intervention. Une majorité des répondants (81,2%, 298/367) se disent satisfaits des services et soins pharmaceutiques reçus dans les deux groupes.

Conclusion: Il a été faisable d'implanter les trois volets de l'intervention sur une période de six mois. Cette intervention est perçue comme étant positive par les parents et les soignants exposés, et la majorité des répondants ont été satisfaits des services et soins pharmaceutiques offerts.

Environmental Contamination with Nine Antineoplastic Drugs in 93 Canadian Centers

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Background: Antineoplastic drugs traces are measured on many surfaces in healthcare centers. A biannual surveillance of antineoplastic traces is recommended in Canadian guidelines.

Objectives: To monitor environmental contamination by nine antineoplastic drugs in Canadian centers. To explore the impact of factors that may be associated with surface contamination.

Methods: Twelve standardized sites were sampled in each participating center after a working day, before any cleaning was performed (six in the oncology pharmacy and six in patient care areas). Each sample was prepared to allow quantification of six antineoplastic drugs (cyclophosphamide, ifosfamide, methotrexate, gemcitabine, 5-fluorouracil, irinotecan) by ultra-performance liquid chromatography-tandem mass spectrometry. Three additional antineoplastic drugs were detected, but not quantified (docetaxel, paclitaxel, vinorelbine). The impact of some factors was evaluated with a Kolmogorov-Smirnov test for independent samples.

Results: Ninety-three Canadian centers participated in 2019 with 1045 surfaces sampled, 551 in pharmacy and 494 in patient care areas. Cyclophosphamide was most often measured on surfaces (32.4% positive samples, 75th percentile=0.0017 ng/cm², 90th percentile=0.021 ng/cm²) followed by gemcitabine (20.3% positive samples, 75th percentile<limit of detection (LOD), 90th percentile=0,0059 ng/cm²) and 5-FU (8.5% positive samples, 75th and 90th percentile<LOD). The front grille inside the hood (81.5% of samples positive for at least one antineoplastic drug), the arm rest (75.8%), the floor in front of the hood (65.2%) and the storage shelf (55.4%) were more frequently contaminated. Traces of all antineoplastics but one (docetaxel) were detected. Centers with a higher number of oncology inpatient and outpatient beds, who prepared more antineoplastic drugs per year and used more cyclophosphamide per year had higher concentrations of cyclophosphamide on their surfaces ($p<0.0001$).

Conclusions: Some working surfaces were frequently contaminated despite the implementation of safe handling guidelines. The use of personal protective equipment remains essential. Environmental monitoring can help centers to monitor their practices and identify contaminated areas.

Environmental Scan of Hospital Pharmacist Participation in Research in Canada

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Background: There is interest and need to encourage Canadian pharmacists to conduct hospital pharmacist-driven research activities (HPDRA), but barriers and opportunities need to be assessed.

Objective(s): Describe hospital pharmacists' participation in research, existing models of pharmacy research units (PRU) and funding opportunities for HPDRA in Canada.

Methods: A bilingual cross-sectional validated survey (Survey Monkey™) was e-mailed to pharmacy directors of Canadian hospitals with ≥ 200 acute care adult or pediatric beds. Participants were given 4 weeks to complete anonymously the 38 question survey and 3 reminders were sent. The research ethics board approved the study. Descriptive statistics are presented.

Results: The survey response rate was 40% (42/104). Sixty percent of respondents were from academic teaching hospitals. The median number of pharmacists per hospital was 43. Sixty-four percent (n=27) of hospitals had pharmacists participating in HPDRA. Only these were asked to respond to the full survey. Amongst these hospitals, the median number of research projects conducted was 9.0 (IQR: 2.5-18.8) over the last 2 years. Approximately half were pharmacy residency projects. The most common types of projects were pharmacy practice, retrospective, drug utilization and prospective cohort or observational studies. The majority of departments published at least 1 manuscript in peer-reviewed journals in the last year, with 25% publishing > 10. The key barriers identified by the directors of pharmacy were lack of dedicated time, research grants, research training and resources. Sixty-five percent of hospitals had some pharmacists with dedicated time for research. Only 5 hospitals had a PRU. The median annual research budget was 17 500$ (IQR: 0 – 76 250$) and the main source of funding was the general pharmacy budget.

Conclusion(s): HPDRA across Canada are modest due to important barriers and limited budgets. Few hospital pharmacy departments have developed a PRU offering resources to facilitate research.

Pharmacists' Experience, Motivation, Attitudes, Self-Perceived Competence and Training Needs to Conduct Pharmacist-Driven Research in a Tertiary Care Teaching Hospital

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Background: Pharmacists in our institution are encouraged to conduct research activities.

Objective(s): Describe hospital pharmacists' research experience as principal or co-investigator in the last 5 years, and their motivation, attitudes, barriers, facilitators, self-perceived competence and training needs regarding research.

Methods: A bilingual validated cross-sectional survey (Survey Monkey™) was e-mailed to all pharmacists employed at a tertiary care teaching hospital. Participants were given 4 weeks to complete anonymously the 41 question survey and 3 reminders were sent. The study was approved by the research ethics board. Descriptive statistics are presented.

Results: The survey response rate was 58% (60/104). The median pharmacist work experience was 9.0 (IQR: 4.0-20.8) years. In the last 5 years, 63% had participated in research activities. Of these and over this period, 69% had published at least one research manuscript and only 5 had received research funding (median 0$; range 0-15 000$) as principal investigator. The median devoted research time was 5 hours (IQR 0-80) per month and the most common types of study designs were descriptive and observational. Most pharmacists (86%) would like greater involvement in research activities and 76% agree that participation in research activities is important to the pharmacy administration. The most common barriers identified by respondents were lack of time, large clinical workload and insufficient staff / resources while potential facilitators included dedicated time in schedule, hiring research resources and pharmacy research mentorship. Pharmacists rated themselves as not very (35%) or moderately (60%) competent to conduct research. Significant training needs identified are statistics, preparation of a grant application and coordinating studies.

Conclusion(s): Our pharmacists are highly motivated to conduct research but require dedicated time, research resources and additional training in statistics and methodology, as well as support in grant application and study coordination.

Disseminated Intravascular Coagulation and Autoimmune Hemolytic Anemia with Oxaliplatin Treatment for Metastatic Colon Adenocarcinoma: A Case Report

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Background: Oxaliplatin is a platinum alkylating chemotherapeutic agent commonly used in the treatment of colorectal cancer. In rare cases, disseminated intravascular coagulation (DIC) and autoimmune hemolytic anemia (AIHA) have been reported with oxaliplatin use. DIC is characterized by the intravascular activation of coagulation, causing microvascular damage to end organs, often overwhelming the coagulation cascade leading to bleeds. AIHA is the autoimmune-mediated destruction of red blood cells (RBCs) by antibodies. Management of both conditions relies on limited evidence from clinical trials in combination with clinical experience.

Case Description: This case describes a 53 year old female undergoing treatment with capecitabine, oxaliplatin, and bevacizumab for adenocarcinoma of the colon. Immediately post-oxaliplatin infusion the patient experienced large volume emesis and a vasovagal episode. Laboratory findings were suggestive of a new coagulopathy and anemia. The patient was diagnosed with AIHA and DIC, and was successfully treated with high dose steroids, transfusions, as well as temporary hemodialysis.

Assessment of Causality: It is probable in this case that DIC and AIHA could be secondary to oxaliplatin, as these adverse events occurred after administration, and resolved after discontinuation. The Naranjo Scale gives DIC four points and AIHA seven points, making these reactions possible and probable, respectively.

Literature Review: Only 1 case report was found that included both DIC and AIHA related to oxaliplatin. Two case reports were identified describing DIC related to oxaliplatin in patients with metastatic colon adenocarcinomas, and 5 case reports were identified for AIHA alone. The Health Canada Adverse Event Reporting Database contained 4 reports of oxaliplatin associated AIHA.

Importance to Practitioners: Oxaliplatin is commonly used for the treatment of colorectal adenocarcinomas and other malignancies. Practitioners should be aware of rare adverse events associated with oxaliplatin such as DIC and AIHA, in order to provide timely treatment and prevent significant morbidity and mortality.

Impact of Ultrafiltration on Tobramycin Clearance and Dosing

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Background: Treatment of serious Gram negative infections with aminoglycosides requires achieving strict peak and trough concentrations to optimize efficacy while reducing risk of adverse effects. Dosing to maintain these targets in patients on hemodialysis and ultrafiltration can be challenging as aminoglycoside clearance is highly variable and depends on dialysis type, filter used and duration. Ultrafiltration (UF) is the process by which water is removed. This is done by means of solute movement across a semipermeable membrane from the area of higher concentration (blood) to lower concentration (ultrafiltrate).

Case description: Nineteen year-old female with complex medical history significant for CNS hemophagocytic lymphohistiocytosis (HLH) and CKD secondary to prior immunosuppressant therapy on intermittent hemodialysis. Tracheal aspirate cultures positive for multi-drug resistant *Pseudomonas aeruginosa* sensitive to gentamicin and tobramycin. During the course of tobramycin therapy, patient required a session of UF. Drug level evaluation was undertaken to appreciate the impact of UF on tobramycin clearance and whether an additional post-UF dose would be required.

Assessment of causality: Patient received usual hemodialysis session on August 30th after which a dose of tobramycin 90mg was administered intravenously. Peak serum concentration was measured to be 7.97 mg/L (target 8-10 mg/L). On August 31st, a 2 hour UF session was performed. Tobramycin serum levels were collected in the morning prior to UF and again that evening after UF. Pre-UF level was 5.31 mg/L and post-UF level was 3.65 mg/L. As the post-UF level was greater than the usual trough target of <1 mg/L, an additional tobramycin dose was not ordered.

Literature review: There is a paucity of current literature detailing the rate of tobramycin by UF specifically.

Importance to Practitioners: A single session of UF in this patient did not alter tobramycin clearance in such a way that additional dosing was needed.

Ceftaroline Monotherapy for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infective Endocarditis: Case Report

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Background: Ceftaroline is a 5th generation cephalosporin with broad spectrum activity against gram positive and negative bacteria including Methicillin-Resistant Staphylococcus aureus (MRSA). It is indicated for complicated skin and soft tissue infections and community-acquired pneumonia. Case-reports have shown clinical success treating bacteremia and endocarditis caused by MRSA when combined with daptomycin. This case report describes a case of MRSA bacteremia and infective endocarditis treated with ceftaroline monotherapy.

Case Description: A 51 year old male presented to hospital with MRSA bacteremia secondary to a diabetic foot ulcer. He was initially treated with vancomycin which was changed to daptomycin after developing acute on chronic renal failure. He was discharged on daptomycin therapy and re-presented to hospital 2 weeks later with MRSA positive blood cultures. He declined clinically with recurrent fevers and positive blood cultures reporting increased resistance to daptomycin. Transesophageal echocardiogram confirmed implantable cardioverter defibrillator (ICD) infective endocarditis. Ceftobiprole was added to the daptomycin regimen, but blood cultures remained positive. The ICD was extracted, ceftobiprole was changed after 4 days of therapy to ceftaroline due to concerns of possible MRSA resistance, and daptomycin was discontinued due to elevated creatinine kinase. Subsequent cultures returned negative. He clinically improved and continued 6 weeks of ceftaroline monotherapy.

Assessment of Causality: Blood cultures drawn during ceftobiprole therapy remained positive. After treatment was changed to ceftaroline and the ICD was removed cultures returned negative and microbiological cure was achieved.

Literature Review: An *in vitro* study showed ceftaroline was more potent than ceftobiprole against MRSA. A 1-year surveillance study in Italy described an MRSA ceftobiprole resistance rate of 12%. One published

case series reported clinical success with ceftaroline monotherapy as salvage therapy for MRSA bacteremia and endocarditis.

Importance to Practitioners: Ceftaroline monotherapy is a treatment alternative for MRSA infective endocarditis, where vancomycin and daptomycin cannot be used.

Description des activités réservées de la Loi 41 réalisées par les pharmaciens dans un hôpital universitaire

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Contexte : La loi 41 permet d'élargir le rôle et l'autonomie du pharmacien. Peu de données objectives sont publiées quant à son application en établissements de santé et son application n'est pas encore très répandu dans la pratique.

Objectifs : Décrire les activités réservées de la Loi 41 réalisées par les pharmaciens dans centre hospitalier universitaire. Décrire l'impact clinique des actes de la Loi 41 (majeur, significatif, mineur, non déterminé).

Méthodologie : Étude rétrospective recensant les neuf activités réservées de la Loi 41 sur une période de 13 jours, du 5 au 21 décembre 2018. Les actes réalisés étaient identifiés à partir des rapports des pharmaciens œuvrant dans les secteurs cliniques. Le dossier patient électronique et le dossier pharmacologique informatisé ont été utilisés pour réaliser la collecte de données. L'analyse statistique était de nature descriptive. L'impact clinique des activités a été déterminée à partir d'une échelle connue. L'étude a été approuvée par le comité d'éthique.

Résultats : Parmi les 1291 patients ciblés, 172 ont eu au moins un acte réalisé pour un total de 336 actes documentés. Les principales activités réalisées ont été la prescription d'une analyse de laboratoire (29,2%;n=98), la prolongation d'une ordonnance (23,5%;n=79), la modification de la dose afin d'assurer la sécurité (20,0%;n=67) et la modification de la posologie (12,2%;n=41). L'impact clinique a été évalué comme étant majeur (14,6%;n=49), significatif (72,3%;=243) et mineur (12,8%;n=43).

Conclusion : Les pharmaciens réalisent quotidiennement les activités réservées de la Loi 41 dans le centre hospitalier universitaire. Trois types d'actes de la Loi 41 comptent pour 73% des activités réalisées. L'impact clinique est majoritairement significatif pour les actes réalisés. Les données colligées confirment l'élargissement du rôle du pharmacien en établissement de santé.

Terbinafine Induced Thrombotic Thrombocytopenic Purpura

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Background: Thrombotic Thrombocytopenic Purpura (TTP) is a medical emergency that is almost always fatal if not properly treated. It presents as thrombocytopenia, microangiopathic hemolytic anemia, and often signs of end-organ damage. It is caused by autoantibodies directed at ADAMTS13, a von Willebrand factor-cleaving protease, resulting in small-vessel platelet-rich thrombi. Autoantibody production can be hereditary, or acquired from certain disease states or medications.

Case Description: A 78 year-old woman presented with a 5-day history of increasing malaise, fatigue, and altered mentation. Her laboratory results were consistent with hemolysis in addition to profound thrombocytopenia, which was suspicious for TTP. The ADAMTS13 activity level was less than 1% and ADAMTS13 inhibitor level was greater than 94 U/mL. ADAMTS13 inhibitor values above 15 U/mL in the context of ADAMTS13 activity values below 10% are diagnostic of TTP. The patient was initiated on daily plasma exchange and prednisone. The patient's only medication on admission was oral terbinafine, which was started 4 weeks prior to admission. It was felt that TTP was likely induced by terbinafine, which was therefore discontinued. The patient responded well to therapy and was discharged home 11 days later.

Assessment of Causality: The Naranjo score for this adverse drug reaction is 7, indicating that TTP was probably caused by terbinafine.

Literature Review: Three cases of oral terbinafine induced TTP were submitted to the Health Canada Reporting Database in the 1990s. Only 1 published case report was found in the literature. However, the drug product monograph was updated in January 2017 to include TTP as a possible ADR after some reported cases.

Importance to Practitioners: TTP is associated with a high mortality. Therefore, it is important for practitioners to promptly recognize this rare drug-induced reaction, discontinue the medication and provide treatment. With proper management, survival rates up to 90% are possible.

Gemcitabine-Associated Atypical Hemolytic-Uremic Syndrome Treated with Eculizumab

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Background: Atypical Hemolytic-Uremic Syndrome (aHUS) is a potentially life-threatening thrombotic microangiopathy (TMA) characterized by anemia, thrombocytopenia, and renal failure. It can be drug-induced and is caused by uncontrolled activation of the complement system. Management of drug-induced aHUS usually involves plasmapheresis. Eculizumab, a monoclonal antibody that inhibits the complement cascade, has also been used. This case report details the successful management of gemcitabine-induced aHUS treated with eculizumab.

Case Description: A 41-year-old female with hepatic cholangiocarcinoma was started on a regimen of cisplatin and gemcitabine. Eight months into the regimen, the treatment was stopped due to a splenic infarct, significant vision changes, new onset hypertension, thrombocytopenia, elevated lactate dehydrogenase (LDH), and serum creatinine peaking at 375 umol/L. Plasmapheresis was started with minimal effect. On day 9, eculizumab was started and her platelet count, LDH and renal function significantly improved. She received 3 months of treatment with eculizumab at which time it was stopped.

Assessment of Causality: This case of aHUS would receive a score of 4 on the Naranjo Scale indicating a possible association with gemcitabine.

Literature Review: Gemcitabine-associated aHUS has been documented in 107 cases, with approximately 15% classifying it to be a definite or probable cause. It has a reported incidence of 0.02-2.2% and a mortality rate of up to 60%. There is no high-quality evidence showing benefit of plasmapheresis for aHUS. Eculizumab has been shown to improve renal function, platelet count, and hemolysis in observational studies.

Importance to Practitioners: Gemcitabine is commonly used to treat solid tumor cancers. Albeit rare, Gemcitabine-associated aHUS can lead

to significant morbidity and mortality if left untreated. Timely diagnosis and treatment are crucial to minimize complications such as end stage renal disease and death. Early initiation of eculizumab may be beneficial as plasmapheresis has been shown to be minimally effective in these cases.

Stability of Morphine Solutions of 20mcg/mL, 40mcg/mL 100mcg/mL 200mcg/mL, 1,000mcg/mL in Syringes Following Dilution with 0.9% Sodium Chloride at Room Temperature (25°C)

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Background: Paediatric patients require lower concentrations of continuous infusions than adults and while previous publications have demonstrated the stability of morphine, data for lower concentrations stored in syringes for more than 14 days is not available.

Objective: To evaluate the chemical stability morphine prepared in syringes at 5 concentrations following dilution in saline and stored in syringes at room temperature.

Methods: On study day 0, 3 units of each of 5 concentrations were prepared and stored at room temperature. Concentration and physical inspection were completed on study days 0, 2, 7, 14, 21, 28,42,56,72, and 91. Morphine concentrations were determined by a validated stability-indicating liquid chromatographic method with UV detection. The maximum chemical stability was determined based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration.

Results: The analytical method separated degradation products from morphine such that the concentration was measured specifically, accurately (deviations from known averaged 2.17%) and reproducibly (replicate error within a day averaged 0.45% and between days averaged 1.09%). A second estimate of between-days reproducibility, the standard deviation of regression averaged 0.64%. During the study period all solutions retained more than 98.42% of the initial concentration in vials and syringes at both temperatures and concentrations. Multiple linear regression (capable of detecting differences of 0.54%) revealed significant differences in percent remaining due to study day (p=0.013) and concentration (p=0.001). The calculated maximum stability exceeded the 91-day study period for all concentrations.

Conclusions: We conclude that morphine concentrations between 20mcg/mL and 1,000mcg/mL are physically and chemically stable for at least 91 days at room temperature (25°C) in syringes. When establishing a BUD, both the stability of the components and the sterility limits established by NAPRA/USP 797 must be considered.

Stability of a New Generic Formulation of Bortezomib Injection (Apotex Brand) in Vials and Syringes Stored at 4°C and Room Temperature (25°C)

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Background: New generic versions of bortezomib raise questions about the reliability of extending stability study data between brands.

Objective: To evaluate the stability of Apotex-bortezomib formulation reconstituted with 0.9% sodium chloride (NS) to produce concentrations of either 1.0 or 2.5mg/L during storage over 42 days at room temperature (25°C) and at 4°C in syringes and manufacturer vials.

Methods: On study day 0, 1.0 and 2.5mg/mL concentrations of the Apotex formulation were prepared. Three units of each container were stored at 25°C and three were stored at 4°C. Concentration and physical inspection were completed on study days 0,1,4,8,11,15,18,21,28,35 and 42. Bortezomib concentrations were determined by a validated stability indicating liquid chromatographic method with UV detection. The recommended beyond use date (BUD) was determined based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration.

Results: The analytical method separated degradation products from bortezomib such that the concentration was measured specifically, accurately (deviations from known averaged 2.17%) and reproducibly (replicate error averaged 0.44% within-days and 2.19% between-days). A second estimate of between-days reproducibility, the standard deviation of regression of study samples, average 1.06%. Multiple linear regression revealed significant differences in percent remaining due to study day (p<0.001) and temperature (p=0.001), but not container (p=0.117) or concentration (p=0.223). Apotex-bortezomib retained >90% of its initial concentration for the duration of the 21-day period for all temperatures, containers, and concentrations.

Conclusions: Apotex-bortezomib formulation reconstituted with NS to concentrations of 1.0 and 2.5mg/mL are physically and chemically stable for at least 42 days at 25°C or 4°C in both syringes and the original manufacturer's glass vials. When establishing a BUD, both the stability of the components and the sterility limits established by NAPRA/USP 797 must be considered.

Stability of a New Generic Formulation of Bortezomib Injection (MDA Brand) in Vials and Syringes Stored at 4°C and Room Temperature (25°C)

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Background: New generic versions of bortezomib raise questions about the reliability of extending stability study data between brands.

Objective: To evaluate the stability of MDA-bortezomib formulation reconstituted with 0.9% sodium chloride (NS) to produce concentrations of either 1.0 or 2.5mg/L during storage over 21 days at room temperature (25°C) and at 4°C in syringes and manufacturer vials.

Methods: On study day 0, 1.0 and 2.5mg/mL concentrations of the MDA formulation were prepared. Three units of each container were stored at 25°C and three were stored at 4°C. Concentrations were determined and physical inspections were completed on study days 0,1,2,5,7,11,14,18 and 21. Bortezomib concentrations were measured by a validated stability -indicating liquid chromatographic method with UV detection. The maximum chemical stability was determined based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration.

Results: The analytical method separated degradation products from bortezomib such that the concentration was measured specifically,

accurately (deviations from known averaged <2%) and reproducibly (replicate error averaged <1% within-days and <2% between-days). A second estimate of between-days reproducibility, the standard deviation of regression of study samples, averaged 1.0%. Multiple linear regression revealed significant differences in percent remaining due to study day ($p<0.001$) and temperature ($p<0.001$), but not container ($p>0.02$) or concentration ($p>0.2$). MDA-bortezomib retained >90% of its initial concentration for the duration of the 21-day period for all temperatures, containers, and concentrations.

Conclusions: MDA-bortezomib formulation reconstituted with NS to concentrations of 1.0 and 2.5mg/mL are physically and chemically stable for at least 21 days at 25°C or 4°C in both syringes and the original manufacturer's glass vials. When establishing a BUD, both the stability of the components and the sterility limits established by NAPRA/USP 797 must be considered.

Stability of 3.33 mg/mL Bicalutamide in Syringes and Amber Plastic Bottles Following Reconstitution with Sterile Water or Oral Mix Sugar Free at 4°C and Room Temperature (25°C)

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Background: A commercial bicalutamide suspension is not available in Canada and the stability of an extemporaneous formulation has not been previously reported.

Objective: To evaluate the stability of 3.33mg/mL bicalutamide prepared in sterile water (SW) or suspended in Oral Mix Sugar Free – Medisca (OMSF) during storage over 90 days at room temperature (25°C) or refrigerated (4°C) in plastic syringes and amber plastic bottles.

Methods: On study day 0, bicalutamide (Accord) 3.33mg/mL suspensions were prepared. Three units of each container were stored at room temperature and 3 were stored in the refrigerator. Concentration and physical inspection were completed on study days 0,2,7,14,21,28,42,56,72, and 90. Bicalutamide concentrations were determined by a validated stability-indicating liquid chromatographic method with UV detection. The maximum chemical stability was determined based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration.

Results: The analytic method separated degradation products from bicalutamide such that the concentration was measured specifically, accurately (deviations from known averaged 2.02%) and reproducibly (replicate error within-a-day averaged 0.35% and between-days averaged 0.98%). A second estimate of between-day reproducibility, the standard deviation of regression of study samples, averaged 1.10%. Multiple linear regression did not identify any significant differences in percent remaining to container ($p=0.06$), diluent ($p=0.37$), temperature ($p=0.46$), or study date ($p=0.96$). The study was capable of detecting a 0.99% difference in concentration due to study day, temperature, container, or diluent. The bicalutamide suspension retained >90% of its initial concentration for the 90-day period for all temperatures, diluents and containers.

Conclusion: We conclude that a 3.33mg/mL bicalutamide suspension prepared with SW or OMSF is physically and chemically stable for at least 90 days at 4°C or 25°C in plastic syringes or amber plastic bottles.

Chemical Stability of Epinephrine Diluted in 0.9% Sodium Chloride and Stored in Polypropylene (PP) Syringes at 4°C and 25°C

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Background: A previous publication has demonstrated the stability of 25, 50 and 100 mcg/mL epinephrine solutions for 30 days, but not concentrations as low as 10 mcg/mL.

Objective: To evaluate the chemical stability epinephrine prepared in syringes at concentrations of 10 mcg/mL diluted in 0.9% sodium chloride (NS) at both room temperature (25°C) and under refrigeration.

Methods: On study day 0, 10mL solutions of 10 mcg/mL epinephrine diluted in NS were prepared and stored in BD syringes. 3 units of each container and concentration were stored at room temperature and 3 were stored at 4°C. Concentration analysis was completed on study days 0,2,7,14,21,28,42,56,72 and 91 using a validated stability-indicating liquid chromatographic method with UV detection. Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration (T-90).

Results: The analytical method separated degradation products from epinephrine such that the concentration was measured specifically, accurately (deviations from known averaged 2.13%) and reproducibly (within-day replicate error averaged 0.48%(CV(%)). During the study period all solutions at 4°C retained more than 89.62% of the initial concentration for 91 days. Solutions stored at 25°C retained more than 90% for 21 days. Multiple linear regression revealed significant differences in percent remaining due to study day ($p=0.00002$) and temperature ($p=0.00186$). The calculated T-90, with 95% confidence, was 71.40 days for solutions stored at 4°C but only 12.77 days for solutions stored at 25°C.

Conclusions: We conclude that 10 mcg/mL epinephrine solutions diluted in NS stored at 4°C is chemically and physically stable for 64 days, with 95% confidence. This allows the syringe to be held at room temperature for up to 24 hours during this period and still retain more than 90% of the initial concentration.

Compatibility and Stability of Ketamine and Ringers Lactate at Room Temperature (25°C)

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Background: IV Ketamine is widely used in our institution for both pain and sedation. However, many patients also receive an infusion of Ringers lactate. Compatibility of ketamine with Ringer's is unknown.

Objective: To evaluate the compatibility and stability of 1.5 and 7.6 mg/mL solutions of ketamine with Ringers lactate across a range of infusion rates at room temperature.

Methods: Ketamine solutions in saline, intended for infusion at rates between 2.6 and 99 mL/hr were mixed with Ringer's solutions intended for infusion at rates between 25 and 200 mL/hr. Solutions were evaluated for precipitate, changes in colour, temperature and evolution of gas at multiple times over a 24-hour period. To confirm compatibility, the stability and compatibility of ketamine concentrations of 1.5 and 7.6 mg/mL diluted directly in Ringer's lactate was evaluated at room temperature over 36 hours. Ketamine concentrations were determined

by a validated stability-indicating liquid chromatographic method with UV detection. The maximum chemical stability was determined based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration.

Results: The analytic method separated degradation products from ketamine such that the concentration was measured specifically, accurately (deviations <2.0%) and reproducibly (<2%). In compatibility studies, changes in mixed solutions did not occur over the 24 hour period. In the stability study, ketamine solutions remained greater than 97% of the initial concentration over the 36 hour study period (chemical stability >36-hours) and no physical incompatibility was evident.

Conclusion: We conclude that 1.5 and 7.6 mg/mL concentrations of ketamine in Ringer's are physically compatible and chemically stable over 36 hours at room temperature. Furthermore, 1.5 and 7.6 mg/mL infusions of ketamine in saline are physically compatible with Ringers lactate infusions over 24 hours.

Retrospective Review of Vancomycin Dosing for Non-Central Nervous System Infections in Patients Admitted to the Neonatal Intensive Care Unit

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Background: Vancomycin is a common antibiotic prescribed in the neonatal intensive care unit (NICU) for gram-positive infections. However, achieving vancomycin therapeutic range is challenging in neonates, which led to revisions to our vancomycin dosing guideline in 2017.

Objectives: We evaluated the ability of the current vancomycin dosing guideline to achieve serum vancomycin therapeutic trough concentrations of 5-12 mg/L to treat non-central nervous system (CNS) infections in the NICU. We also assessed efficacy and safety outcomes of vancomycin courses.

Methods: A retrospective chart review was conducted on neonates admitted to the NICU and received vancomycin for suspected or documented non-CNS infections between April 1, 2017 and May 31, 2018. Patient baseline characteristics, vancomycin dose, trough concentrations and relevant laboratory results were collected.

Results: Total of 144 neonates or 169 vancomycin courses (77% empiric treatment and 23% for documented infections) were evaluated. Therapeutic vancomycin concentrations at steady state were achieved in 67% of neonates with post-menstrual age (PMA) <27 weeks who started vancomycin at 24 mg/kg/dose IV q24h, 66% of neonates with PMA of 27-36 weeks, who received 18 mg/kg/dose IV q12h and 57% of neonates with PMA ≥37 weeks dosed at 22.5 mg/kg/dose IV q12h. Over 30% of neonates with PMA <27 weeks or ≥37 weeks had subtherapeutic concentrations. Statistically significant decline in C-reactive protein was observed regardless of whether the first vancomycin concentration was subtherapeutic, therapeutic or supratherapeutic (p<0.05). No nephrotoxicity was observed based on serum creatinine, blood urea nitrogen or urine output.

Conclusions: Revised vancomycin dosing guideline led to increased proportion of patients achieving vancomycin therapeutic range at initial dose (64% vs. 49% using previous dosing guideline). However, vancomycin dosing can still be further optimized, especially for patients with PMA <27 weeks or ≥37 weeks using a pharmacokinetic model with considerations of relevant covariates.

Trends in Antimicrobial Resistance for *Enterobacter* spp. Collected from Inpatients at a Major Canadian Tertiary Care Center: A Retrospective Analysis over 14 Years

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Background: *Enterobacter* are opportunistic pathogens and a common cause of nosocomial infection. A recent study examined susceptibility trends among 719 *Enterobacter cloacae* isolates submitted to the CANWARD surveillance program between 2007-2016 and found resistance to ceftazidime, ceftriaxone, ertapenem, meropenem, and co-trimoxazole increased over time when a univariate test for trend was applied.

Objective: To evaluate antimicrobial resistance trends among *Enterobacter* isolates collected at Sunnybrook Health Sciences Center (SHSC) and compare findings to national CANWARD trends.

Methods: Susceptibility data for *Enterobacter* clinical isolates collected between October 2002 to September 2016 were retrospectively extracted from the SHSC Microbiology database. Univariate linear regression was used to evaluate changes in the percentage of isolates resistant to various antimicrobials at a significance level of 0.05.

Results: A total of 3181 *Enterobacter* isolates were identified across the 14-year study period (72% *E. cloacae* complex; 26% *E. aerogenes*; 2% other *Enterobacter* spp.). The majority of isolates grew from cultures drawn greater than 48 hours after admission (70%). Forty-eight percent were collected from ward patients, 35% from ICU patients, and 17% from patients in the emergency room. Resistance to ciprofloxacin, gentamicin, and tobramycin decreased across the study period (-0.6% resistant/year, p=0.0252; -1.0% resistant/year, p=0.0041; -1.0% resistant/year, p=0.0029; respectively). A signal suggesting reduced co-trimoxazole resistance was detected (-0.7% resistant/year, p=0.0562). In contrast, resistance to meropenem increased (+0.1% resistant/year, p=0.0023), and a signal suggesting increased piperacillin/tazobactam resistance was detected (+1.0% resistant/year, p=0.0566). Resistance to ceftazidime, ceftriaxone, and ertapenem remained relatively stable.

Conclusion: Increasing rates of meropenem resistance were found for CANWARD and SHSC *Enterobacter* isolates when univariate tests were applied; however, resistance trends for other antimicrobials differed between the SHSC and CANWARD datasets. Although validation with multivariate analyses is warranted, our findings suggest that knowledge of institutional resistance is important as differences from national trends may exist.

Patterns of Antimicrobial Resistance among *Proteus* Isolates at Sunnybrook Health Sciences Centre: A 14-Year Retrospective Observational Study

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Background: *Proteus spp.* are members of the *Enterobacteriaceae* family and common uropathogens. Wildtype strains of *P. mirabilis* are usually susceptible to ß-lactam antibiotics; however, the number of strains producing extended-spectrum ß-lactamases and AmpC enzymes is on the rise.

Objective: To investigate the antimicrobial resistance patterns among clinical isolates of *Proteus* spp. collected at Sunnybrook Health Sciences Centre (SHSC) over a 14-year study period.

Methods: Patient-level data for clinical isolates of *Proteus* spp. collected from inpatients between October 2002 and September 2016 were extracted from the SHSC Microbiology database and included in this retrospective observational study. Longitudinal trends in the susceptibility of these isolates to various antimicrobial agents were characterized using linear regression at a significance level of 0.05.

Results: Of a total of 1993 *Proteus* isolates identified, 1850 (93%) were *P. mirabilis*, 104 (5%) were *P. vulgaris*, and 39 (2%) were *P. penneri*. Among all isolates, 70% (1840/1993) were resistant to at least one therapeutically active antimicrobial agent. Although the proportion of *P. mirabilis* isolates resistant to piperacillin/tazobactam increased (-0.3% susceptible/year; p<0.001) and a signal suggesting increasing rates of ceftazidime resistance was also detected (-0.3% susceptible/year; p=0.087), the overall susceptibility to piperacillin/tazobactam (~99%) and ceftazidime (~97%) remained high. *P. mirabilis* susceptibility to ampicillin (~81%), cefazolin (~90%), ceftriaxone (~96%), ciprofloxacin (~88%), co-trimoxazole (~87%), gentamicin (~91%), meropenem (~100%), and tobramycin (~93%) remained stable over the 14-year study period. Patterns of resistance for *P. vulgaris* and *P. penneri* could not be reliably determined due to the low number of clinical isolates collected each year.

Conclusion: Antimicrobial resistance patterns of *P. mirabilis* at SHSC remained largely unchanged over the 14-year period assessed. All antimicrobials tested, with the exception of ampicillin, remain appropriate empiric treatment options against *P. mirabilis*.

Assessing the Use of a Standardized Allergy History Questionnaire in Patients with a Reported Penicillin Allergy

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Background: Inappropriate allergy labeling is associated with significant clinical and pharmacoeconomic implications. Detailed allergy assessments are a key component of antimicrobial stewardship and aid in identifying true immediate Type-1 hypersensitivity reactions. The allergy form currently used at the University Hospital of Northern British Columbia (UHNBC) relies on the assessor's unguided ability to ask appropriate prompting questions to obtain a thorough history.

Objective: The primary objective of this study was to compare the quality and quantity of documentation gathered from a standardized allergy history questionnaire to that of the current allergy history form.

Methods: This was a prospective observational study of patients admitted to medical and surgical services at UHNBC with a penicillin-family allergy reported on their Electronic Medical Record. An allergy report was processed using the health information software system and patients were interviewed using a detailed allergy history questionnaire.

Results: Forty percent of patients had an inappropriate allergy label on their EMR. Out of the 48 patients assessed, only 36 had a listed reaction on their EMR. Furthermore, only 36 of the 48 patients had the same allergy reported on the allergy history form in their paper chart, of which 22 had a documented reaction. The mean time to conduct the questionnaire was 2 minutes, ranging from 1 to 4 minutes to complete.

Conclusion: Documentation of allergy histories is often incomplete. Detailed allergy assessments are the first step in identifying true Immunoglobulin E (IgE)-mediated hypersensitivity reactions. Therefore, implementation of a standardized allergy history questionnaire may serve to improve documentation and overall antimicrobial stewardship.

Implementation of Spectrum, an Antimicrobial Stewardship App at a Community Hospital

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Background: Spectrum, an antimicrobial therapy reference app for healthcare professionals, was implemented by the Antimicrobial Stewardship Program (ASP) team to help reinforce appropriate prescribing practices in a community hospital.

Description: The Spectrum app is customized to deliver hospital specific antimicrobial therapy guidelines in an algorithmic format along with pathogen information and antimicrobial drug monographs.

Action: Content for the app was provided by the ASP team based on current guidelines along with local resistance patterns, the hospitals drug formulary, in-house diagnostic methods and the clinical expertise of the hospitals infectious disease physicians and pharmacists. Once content was incorporated into the app, it was reviewed by select Infection Control Practitioners, pharmacists and physicians at the hospital for accuracy and usability. Feedback was obtained and updates made to the content prior to hospital wide roll out. After extensive promotion to potential users the app was officially launched in November 2018.

Evaluation: Uptake of the app has been positive with 398 current active users. The majority of users are physicians or medical residents/students (57%) or pharmacists (22%). A survey was conducted following implementation which demonstrated that users are highly satisfied with the app with more than 90% of respondents scoring 7 or greater on a 10 point satisfaction scale. Appropriate prescribing of azithromycin for community acquired pneumonia was highlighted in the app and a concurrently released preprinted order set. Compared to the same time period in 2017, use of azithromycin was reduced by 29% following implementation.

Implications: Use of the Spectrum app appears to be an effective tool in positively influencing prescribing practices. Content will continue to be updated to encourage ongoing practice change.

Trends in Antimicrobial Resistance of *Citrobacter* Isolates Over a 14-Year Time Period

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Background: Antibiotic resistance is a global healthcare concern. *Citrobacter* spp. are nosocomial gram-negative bacterial pathogens with the potential for multidrug resistance. Unfortunately, because *Citrobacter spp*. have been classified as low priority pathogens, they have received little attention in the published literature.

Objective: To evaluate changes in antimicrobial resistance patterns of *Citrobacter* clinical isolates collected from inpatients at Sunnybrook Health Sciences Centre (SHSC), Toronto, Ontario over a 14-year time period.

Methods: Patient-level data for clinical isolates of *Citrobacter* spp. were retrospectively extracted from the SHSC Microbiology database from October 2002 to September 2016. Annual trends in ciprofloxacin, ceftazidime, ceftriaxone, co-trimoxazole, ertapenem, gentamicin, meropenem, and piperacillin/tazobactam resistance were assessed using linear regression at a significance level of 0.05.

Results: Of 1256 *Citrobacter* clinical isolates identified, 70% were from urine, 9% from blood, 8% from respiratory sources, and 13% from other

human specimens. Isolates were obtained from patients on the wards (52%), in the emergency department (29%), and in intensive care units (19%). Fifty-five percent of isolates were collected after 48 hours of hospital admission, and 45% were collected within 48 hours of admission. The most prevalent species were *Citrobacter freundii* (49%) and *Citrobacter koseri* (32%). Other species included *Citrobacter braakii* (6%), *Citrobacter amalonati* (4%), *Citrobacter farmer* (2%), and undifferentiated *Citrobacter* species (5%). *Citrobacter* spp. remained 100% sensitive to ertapenem and meropenem across the 14-year study period. Significant decreases in co-trimoxazole (-1.0% resistant/year; p=0.006) and gentamicin (-0.7% resistant/year; p=0.006) resistance were detected; whereas resistance to ciprofloxacin, ceftazidime, ceftriaxone, and piperacillin/tazobactam remained stable over time.

Conclusion: This study represents the first in Canada to evaluate changes in antimicrobial resistance of *Citrobacter* to specific antibiotic agents over an extended timeframe. This is valuable information for antimicrobial stewardship practitioners and compliments the growing body of literature on gram-negative bacterial resistance.

Evaluating the Efficacy and Safety of Buprenorphine Microdosing for Opioid Use Disorder: A Systematic Review

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Background: Buprenorphine is a high-affinity partial opioid agonist that can displace full agonists (e.g. heroin) from opioid receptors, precipitating withdrawal. To avoid this, patients are traditionally required to be in moderate withdrawal prior to buprenorphine induction. A novel method that eliminates the need for cessation of the full opioid agonist prior to induction uses microdoses (less than 2 mg) of buprenorphine. Little is known about the efficacy and safety of this method.

Objectives: This systematic review was conducted to determine if buprenorphine microdosing improves adherence and decreases relapse rates compared to traditional induction methods in adults with opioid use disorder.

Methods: A systematic literature search was conducted for all relevant publications using Medline, Embase, and PubMed (from database inception to September 16, 2019). Citations of retrieved articles were screened to identify other relevant articles. Articles were reviewed if buprenorphine induction began with a dose of less than 2 mg and overlapped with full opioid agonist use. Articles were not excluded based on study design.

Results: Seven studies met the inclusion criteria. All were case studies or series, totalling 11 patients. None of the studies had a comparator group or case. Patients were heterogenous with respect to the opioid agonist used, with two patients transitioning directly from methadone to buprenorphine. The microdosing induction duration ranged from three to 129 days. A low incidence of precipitated withdrawal was reported, however objective reporting using a validated tool was inconsistent. Two studies reported adherence rates, with one patient remaining on therapy at day 45, and another relapsed to illicit heroin use at three months.

Conclusions: These studies were heterogenous and commonly lacked objective and long-term outcome reporting. Larger, controlled, long-term studies should be conducted to assess the efficacy and safety of this novel induction method.

Wasting Better: An Interprofessional Evaluation of Narcotic and Controlled Drug Disposal Devices within a Pediatric Teaching Hospital

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Background: National and provincial standards for narcotics (and controlled drugs) require wasted drug to be altered or denatured to such an extent that consumption is impossible or improbable and then incinerated at a licensed facility. Historical adulterants like kitty litter and dish soap were not acceptable. Disposal of these medications in the garbage, sink or in biomedical waste also were not acceptable. Local audits of these standards revealed gaps in staff knowledge and a lack of standardized processes across clinical areas.

Description: Three different marketed narcotic waste devices were identified for use in patient care areas. RxDestroyer(Daniel's) uses an aqueous solution of activated charcoal and accepts anything. The Cactus SmartSink(Stryker) and Cactus PharmaLock (Stryker, liquid only) use absorbent gel, ipecac and other chemicals to render the contents altered and hopefully irretrievable.

Action: An interprofessional project team searched for a solution that for all patient care areas, which met all applicable standards and was simple to use. Clinical teams were presented information about local audits, identified gaps and possible solutions. Volunteers were then requested for participation in the evaluation process.

Evaluation: A pragmatic observational trial was designed to compare device capacity, security features, and user preferences. The devices were placed by consensus, after education and consultation with teams. Participating areas included: medicine, surgery, intensive care, operating rooms and recovery rooms. User experience, preferences and device limitations were captured as comments and quantitative preferences by online anonymous questionnaire. Overall users showed a preference for the Stryker devices. PharmaLock was best for procedural areas. All three devices had some problems reported, including overfilling, spill, and sharps/vials inserted.

Implications: This trial increased awareness about narcotic wasting standards and highlighted limitations of these devices in various clinical settings. Results need to be replicated at an adult site before the process is complete.

Pragmatic Observational Study of the Implementation of Narcotic and Controlled Drug Disposal Devices within a Pediatric Teaching Hospital

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Background: National and provincial standards for controlled substances require wasted drug to be altered or denatured to an extent that consumption is impossible or improbable, and then incinerated at a licensed facility. Historical adulterants like kitty litter and dish soap are not acceptable. Disposal of these medications in the garbage, sinks or in biomedical waste also are not acceptable. Local audits of these standards revealed gaps in staff knowledge and a lack of standardized processes across clinical areas.

Objective: To compare the cost, feasibility and user experience after implementation of narcotic waste devices in a pediatric teaching hospital, three devices were identified for trial. RxDestroyer(Daniel's) uses an aqueous solution of activated charcoal and accepts anything. The Cactus SmartSink(Stryker) and Cactus PharmaLock(Stryker, liquid only) use absorbent gel, ipecac, and other chemicals to render the contents altered and hopefully irretrievable.

Methods: Devices and installation location were selected in consultation with clinical teams. Each clinical area trialed two devices using a side by side or crossover design. Participating areas included inpatient medicine/surgery, intensive care, operating rooms, endoscopy and recovery rooms. User experience was collected using an anonymous online survey. Cost information was calculated using purchase costs, while study staff documented start and end weights for all waste canisters used.

Results: Procedural care areas preferred the PharmaLock device. The medicine/surgery team clearly preferred the SmartSink. Each team used each device for at least 75 days. Estimated disposal standardized to cost per Liter of waste in descending order: 64.80$(RxDestroyer), 32.06(SmartSink), 24.70$(PharmaLock). Amounts of waste generated varied greatly by location.

Conclusions: Liquids represented the vast majority of controlled waste. The most cost effective device was the PharmaLock. The volume of narcotic waste generated drives operating costs. Accurate cost estimates require implementation in an adult hospital.

Opioid Prescribing at Discharge for General Surgery Patients: A Prospective Study

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Background: The overprescribing of opioids is a contributing factor to Canada's opioid crisis. Recent studies have demonstrated that surgery patients generally use less opioids than what is prescribed at discharge.

Objective(s): The goal was to characterize our institution's discharge prescribing practices and correlate it with patient opioid use post-discharge to inform future quality improvement initiatives for optimizing opioid prescribing for general surgery patients.

Methods: A prospective cohort study using telephone questionnaires was performed from January 28 - May 31, 2019. Patient charts were reviewed for baseline characteristics and opioid use 24-hours pre-discharge. Patients were contacted 2 weeks post-discharge to assess their opioid usage, pain management experience, and if they received education for discharge opioid use and appropriate disposal while in-hospital. Data were analyzed using descriptive statistics.

Results: Thirty-five of 45 patients responded to the questionnaire (78% response rate; mean age 59.1 ± 16.1 years; 49% female). Though 33% of patients did not use any opioids in the 24-hours before discharge, all patients were prescribed opioids. On average, patients were prescribed 80.7 milligram morphine equivalents (MME). Ninety-one percent of patients had stopped using opioids at follow-up, and on average 53.5 MME per patient was unused. Though 86% of patients were satisfied with their pain control, 37% felt they had been over-prescribed opioids. Sixty-nine percent of patients received in-hospital education on how to use their discharge opioid, while 14% received education on appropriate disposal of unused medications. None of the patients had disposed their medications at time of follow-up.

Conclusion(s): In the general surgery population, a high proportion of opioids prescribed post-discharge are unused and undisposed, indicating that there is room for improvement for prescribing practices. Strategies to curb excess opioid prescribing and increase proper disposal, such as standardized opioid prescriptions, part fills, and increased inpatient education, should be explored.

Opioid Use Post Discharge from Hip and Knee Arthroplasty

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Background: Post arthroplasty surgery is a major source of opioid prescriptions and excess opioid prescriptions can lead to long-term use and diversion. A better characterization of opioid use may help guide future prescribing.

Objective(s): This quality improvement initiative aimed to describe opioid use in patients discharged from hip or knee arthroplasty, and to describe the relationship between outpatient opioid use, reported pain scores, and inpatient post-operative opioid consumption.

Methods: Patients undergoing elective hip or knee arthroplasty discharged with an opioid prescription were recruited for a telephone survey 2-3 weeks post discharge to assess opioid use and pain scores. Exploratory analysis compared opioid use in hospital and post discharge, and also compared outpatient opioid use and reported pain scores. All opioid doses were standardized to hydromorphone 1mg tablet equivalents. Paired t-test was used to compare means and Pearson correlation was used to describe correlation.

Results: Fifty-one patients were recruited, and 44 patients completed the survey (23 hip, 21 knee). Patients were prescribed an average of 100 (±38) tablets of hydromorphone 1mg equivalents. On average, patients with knee arthroplasty used 79 (±41) tablets post discharge while patients with hip arthroplasty used 64 (±48) tablets (p=0.28). The average pain score of patients at discharge was 7 (±2). Patients who reported a pain score of 7 or more used significantly more opioid tablets post discharge than patients with a pain score of less than 7 (88 (±44) tablets vs. 42 (±29) tablets, p<0.01). Opioid use in the 24-hour period before discharge was moderately correlated with opioid use post discharge (R^2=0.59, p<0.01).

Conclusion(s): The use of opioids by patients post knee or hip arthroplasty is highly variable. Pain score at discharge, opioid use in the 24-hour period before discharge, and surgery type may be used to individualize prescription quantities.

What Your Pharmacist Can Do for You: A Review of the Pharmacists' Role in an Allogeneic Hematopoietic Transplant Clinic

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Background: Pharmacists in clinic play an essential role in the care of post-allogeneic hematopoietic stem cell transplant (allo-HSCT) patients. Literature describing their role in this multidisciplinary setting is limited.

Objectives: This study aimed to capture pharmacists' activities in the pharmaceutical care of allo-HSCT patients, and to assess patient-perceived value of pharmacists in clinic.

Methods: Predefined selection criteria identified patients to be seen by a pharmacist. Pharmacists collected best possible medication histories (BPMHs), conducted medication reconciliation (MedRec), identified drug therapy problems (DTPs), made clinical recommendations and provided patient counselling. Data was collected from January 2018 to 2019. Patient satisfaction surveys were administered from January 7 to 28, 2019.

Results: The median number of patients per allo-HSCT clinic was 25 (range 6-42) and the median number seen by a pharmacist was 4 (range 1-9). Of those patients seen by a pharmacist, a median of 3 (range 1-8) had BPMH and MedRec completed, and 2 (range 1-6) received pharmacist-led counselling. A total of 806 DTPs were identified. The most common DTPs were: unnecessary drug (278, 34.2%), additional drug therapy required (235, 28.9%) and non-adherence (144, 14.0%). The median number of DTPs identified per clinic was 5.5 (range 1-15). Based on these DTPs, a median number of 6 recommendations were made by the pharmacist per clinic, with 5 being accepted by the prescriber. The overall acceptance rate was 96.4% (787/816). Fifty-six patients from the allo-HSCT clinic participated in the satisfaction surveys. Eighty-seven percent agreed or strongly agreed their interaction with the pharmacist had a positive impact on their care.

Conclusion: The pharmacist plays an integral role in the management of allo-HSCT patients in the ambulatory setting. Pharmaceutical care activities delivered by pharmacists in clinic are valued by both prescribers and patients.

Development and Evaluation of a Diabetes Education Program for Pharmacists

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Background: As part of a broader practice standardization project, an education program was developed focusing on a series of high risk, but commonly seen therapeutic topics. Diabetes management is a complex area of study that requires pharmacists to have minimal baseline knowledge in order to identify and resolve related drug therapy problems (DTPs).

Description: To ensure pharmacists possess the required knowledge and skills, a diabetes education module was developed, implemented and evaluated.

Action: The diabetes education module consisted of a voiced-over slideshow presentation, which included supporting institutional policies and procedures. The education module underwent review and feedback from expert and typical pharmacist users prior to deployment. Assessment of the pharmacist's knowledge and skills consisted of a 20-question multiple choice test that was administered both at baseline and after review of the module. Point-biserial (p-bis) and p-values were used to ensure test question validity and reliability. Pharmacists were required to score at least 80% on the post-module test. Program evaluation consisted of a questionnaire asking about the pharmacist's own confidence and of their colleagues to identify and resolve diabetes-related DTPs, and the perceived value of the program.

Evaluation: Fifty-four pharmacists completed the pre- and post-module tests. Post-module completion, the average test score increased from 80% to 95%. All pharmacists (54/54 [100%]) passed the test. Responses from the post-module questionnaire indicated that pharmacists were overall confident in their own and colleagues' ability to identify and resolve diabetes DTPs, and perceived the program as beneficial to improve patient care and safety.

Implications: The results suggest that pharmacists benefitted from a diabetes education program. Completion of the education module and post-module test are now mandatory for all new staff. Based on the program's success, future modules on different therapeutic topics are in development.

A Drug Use Evaluation of Proton Pump Inhibitors at a Canadian Teaching Hospital

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Background: Harms associated with chronic proton pump inhibitors (PPI) are of increasing concern. Since the 'Choosing Wisely Canada' PPI deprescribing recommendations were released, PPI usage has not been evaluated at our institution. We hypothesized that PPIs were over-utilized and that opportunities exist for use optimization.

Objectives: This study was designed to characterize PPI use in concordance with evidence-based assessment criteria derived from international guidelines.

Methods: A retrospective observational drug use evaluation (DUE) was conducted for a one year period (April 1, 2017 to March 31, 2018) at a Canadian, urban, university-affiliated, tertiary care centre. Inpatients prescribed at least one dose of PPI were included. The primary measures included the volume and characteristics of PPI orders, and the appropriateness of PPI use. Patients were identified using the pharmacy computer system. Patients' electronic charts were reviewed using a standardized data collection form. Descriptive statistical analyses were performed.

Results: A total of 617 patients with 1000 PPI orders were identified. The most common reasons for admission were cardiovascular [164 (27%)] and orthopedic [63(10%)] related. Fifty (8.1%) patients were treated for an UGIB resulting in 212 (21%) PPI orders. Of UGIB orders, 58 (39.7%) pre- and 51 (63.8%) post-endoscopy orders were deemed appropriate. Of non-UGIB orders, the most common indication was gastroesophageal reflux disease (171, 22%). More than half of orders [409/788 (52%)] were deemed to be appropriate based on route and indication. The most common serious PPI-related adverse effects experienced were hospital-acquired pneumonia (n=22) and *Clostridioides difficile* infections (n=10). Of discharge prescriptions for newly-started PPIs in hospital, the majority [153 (75%)] had no documented duration.

Conclusions: Approximately half of all PPI use at our institution was inappropriate. Opportunities to further optimize their use may be explored through order set modification or prescriber education.

Systematic Deprescribing of Proton Pump Inhibitors: Pilot Study in a Geriatric-Medicine Unit at a Community Teaching Hospital

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Background: Proton pump inhibitors (PPIs) are inappropriately prescribed in up to 50% of users. Long-term use of PPIs may be linked to increased risk of Clostridioides difficile infections, pneumonia, dementia, bone fractures and nutrient malabsorption.

Objective: To examine feasibility and impact of a PPI-deprescribing algorithm in alternate level of care (ALC) patients on a geriatric-medicine unit at a community teaching hospital.

Methods: This pilot project was a single center intervention with pre- and post-study design conducted on ALC patients in a geriatric-medicine unit. The primary outcome was composite of patients with PPI stopped or reduced. A PPI deprescribing algorithm was used to standardize deprescribing in eligible patients. A retrospective chart review was completed pre-intervention to determine deprescribing rate. In the intervention, the need for PPI was evaluated through chart review and discussion with patient/family and prescriber(s). In eligible patients, the dose was halved every 2 weeks with monitoring for adverse events until discharge. Patients had 4 week follow up post-discharge. Fisher's exact test was used for statistical analysis.

Results: A total of 72 patients were enrolled (n=36 pre, 36 post). Pre-intervention, 12 patients (31%) had their PPI deprescribed [9 patients (75%) had their PPI stopped, 3 patients (25%) had dose reduced]. Post-intervention, 25 patients (69%) had their PPI deprescribed [18 patients (72%) had their PPI stopped, 7 patients (28%) had dose reduced]. PPI deprescribing increased from 31% pre-intervention to 69% post-intervention (p=0.0043). Rebound symptoms were noted in one patient post intervention (2.7%).

Conclusion(s): A significant increase in PPI deprescribing was noted with intervention. Opportunities to improve feasibility include shortening the taper and reduction in post-intervention monitoring. This PPI deprescribing algorithm was successfully used in a medically stable, geriatric population within an acute care setting, and further research could be conducted to see the impact of widespread institutional use.

Documentation of Best Possible Medication History by Pharmacy Technicians in Ambulatory Care Clinics

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Background: In 2014, the organization implemented electronic Medication Reconciliation (eMedRec) for inpatients. In 2015, eMedRec was implemented in one ambulatory clinic to meet Accreditation standards. In January 2019, 28 ambulatory clinics were identified where "medication management is a major component of care" and where medication reconciliation must be provided.

Description: A key step in medication reconciliation is documenting the Best Possible Medication History (BPMH). Four of the qualifying ambulatory clinics requested that Pharmacy Technicians (Technicians) be trained to do this new work. Pharmacy was tasked to train and deploy Technicians to document the BPMHs for patients at their initial visits with a prescriber.

Action: Five Technicians were selected. BPMH training was a combination of: online education; hands on classroom training and; in clinic training with nurses already familiar with the computer system and task. In addition, Technicians learned how to access a scheduling resource to notify clinic clerks that they had obtained a BPMH. Biweekly meetings with clinic leaders were held to identify and resolve issues. Daily huddles were implemented to monitor completion of work in each clinic and reassign staff if needed to complete assigned work.

Evaluation: Quantity: The organization set a target of 90 % completion of BPMH prior or within 2 weeks prior to the initial visit. In September 2019 Technicians completed BPMHs for 89% of the initial visits. Quality: Since July 2, 2019 Technicians have documented approximately 1500 BPMHs. Since then we have received approximately 6 notes from physicians: 3 requested that the Technicians obtain BPMHs on follow up visits in addition to initial visits; 3 questioned inaccurate medication entries. All concerns were followed up and corrective action taken.

Implications: Utilizing Pharmacy Technicians to document BPMHs is an efficient option for ambulatory clinics.

The Comparison of Medication History Taken by Medical Team versus Pharmacy Team

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Background: Medication history (MH) taking is an essential part of a patient evaluation by medical team (MT) during admission to the hospital. To reduce errors, it's been suggested a pharmacy team (PT) to collect MH.

Objective: To compare the correctness and completeness of medication history taken by MT versus PT.

Methods: One thousand medication histories in 250 patients (4 MHs (1 in Emergency room (ER); 2 by the MT in 6 internal medicine wards (IMWs) (1 by the medical intern and 1 by the medical resident); and (1 by the PT in the IMWs) were reviewed. Patients with at least one home medication were entered into the study. The MH taken by each team was compared for correctness (the list of patient home medications as actually was) and completeness (all 5 drug parameters were recorded: name, dosage, frequency, daily dose, route of administration). Each parameter was scored and then summed up to make the comparisons.

Results: Male patients constituted 66.4% of the patients. Elderly patients (60 to 79 Years) comprised the majority (40.5 %). The range of home medications recorded by PT in MHs were 1-25 with the average (± SD) of 7 (±0.2) per patient, while the range of medications recorded by MT were 0-13 with the average (± SD) of 2.7 (±0.2) in the ER, and 0-18 with the average (± SD) of 4.13 (±0.2) in the IMWs. The correctness of MH by MT in the ER and the IMWs were 20% and 46.5% as opposed to 95.7% by PT. The completeness of MHs taken by MT in ER and the IMW were 20.27% and 47.97% as opposed to 95.78% by PT. Cardiovascular medications were the most problematic drug category (22.35%).

Conclusions: A PT is able to take a MH more correctly and completely than the MT.

Physical Assessment Educational Programs for Pharmacists and Pharmacy Students: A Systematic Review

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Background: Pharmacists continue to expand their scope of practice to include physical assessment (PA) as part of their management of drug therapy.

Objective: To describe programs developed to teach pharmacists/pharmacy students PA and identify factors associated with improved knowledge, confidence, and utilization.

Methods: We performed librarian-assisted searches of MEDLINE, Embase, and CINAHL using the terms "pharmacist", "student", and "physical assessment/examination", supplemented with manual bibliography searches. Studies published exclusively as abstracts were excluded. No language restrictions were applied. We extracted data on design, location, participants, methods of instruction, PA skills taught, assessment, utilization, and follow-up.

Results: The search yielded 526 citations, which were independently reviewed by 2 authors. Twenty-seven articles were reviewed in full and 15 were included. Most studies were conducted in the United States or Canada. Twelve studies enrolled pharmacy students (primarily second- or third-year), which focused on comprehensive PA skills or blood pressure measurement. Length of instruction ranged from a single session to a full-year course. Generally, any type of instruction improved knowledge and perceived importance of PA. Students preferred pharmacist instructors to other clinicians, and live subjects to simulators/manikins. Three studies evaluated courses for practising pharmacists, which included comprehensive PA instruction and consisted of 2-30 contact hours. Participants' confidence with performing PA improved in pre- to post-course surveys. One study showed improved confidence with performing PA 6 months after the course, while another study showed no improvement in confidence, but increased PA use, at 6 months post-course. Utilization of PA at after 6 months ranged from 49-65%.

Conclusions: A variety of programs have been developed to teach PA skills to pharmacists/pharmacy students. Broadly, sessions that included pharmacist instructors and live subjects to practice PA skills were preferred. Courses for practising pharmacists improved confidence with performing PA, but persistent confidence and utilization at 6 months were variable.

Exploring Medication Safety Culture in New Brunswick Pharmacies Using the Medication Safety Culture Indicator Matrix

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Background: Medication Safety Culture Indicator Matrix (MedSCIM) is a validated tool that is used to assess patient safety culture within a healthcare setting by inspecting the narrative information presented in medication incident reports.

Description: The objective of this study was to explore the medication safety culture in New Brunswick pharmacies by applying MedSCIM to assess medication incidents that reached patients.

Action: A total of 146 medication incidents involving patients anonymously reported by New Brunswick pharmacy professionals from January to June 2019 were included in this assessment. Using MedSCIM, we performed descriptive statistics and exploratory data analysis on the incidents.

Evaluation: Based on MedSCIM, maturity of patient safety culture can be measured by a two-dimensional 3-by-4 matrix: (1) Core Event Degree of Documentation (where 1 = fully complete; 2 = semi-complete; and 3 = incomplete report) and (2) Maturity of Culture to Medication Safety (where A = generative; B = calculative; C = reactive; and D = pathological). Of the 146 incidents that reached patients, the most common alphanumeric score was 2C (33%). Ratings 1C, 2B, and 1B were also relatively common, together accounting for 39% of the incidents. Eleven of the 146 incidents were associated with either mild or moderate patient harm. Of these, the vast majority (73%) were assigned a Level 1 rating, indicating that the documentation of most harm incidents were complete and included pertinent contributing factors.

Implications: Our MedSCIM analysis reveals that there is still work to be done to facilitate medication safety culture towards a more "system-oriented" or "generative" attitude. Our project offers a baseline or current view of medication safety culture in New Brunswick as the provincial mandatory medication incident reporting practice directive was recently implemented in November 2018. Striving for a "generative" safety culture can ultimately lead to optimization of patient outcomes.

An Assessment of Safety Culture in Saskatchewan Pharmacy Practice

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Background: As the scope of pharmacy practice is expanding, there is a growing interest to measure pharmacy professionals' attitudes on issues that pertain to patient safety as they impact patient outcomes and health care costs.

Description: The objective of this project was to explore the current perceptions and attitudes on patient safety culture in practice by Saskatchewan pharmacy professionals.

Action: We administered a 40-item online questionnaire, which was adapted from a validated Safety Attitude Questionnaire (SAQ) with 6 domains that could influence safety culture, to all 1262 registered pharmacy professionals in Saskatchewan. We conducted descriptive statistics and qualitative thematic analysis, accordingly, on the responses collected.

Evaluation: We collected 230 responses (210 pharmacist respondents and 20 pharmacy technician respondents) with an overall response rate of 18.23%. Pharmacy professionals had a fairly positive perception of safety culture in practice overall, scoring especially high in the domains of teamwork and safety culture. However, there was a concern with the level of staffing and inadequate training and supervision of new pharmacy personnel at the workplace, particularly regarding the integration of recently graduated pharmacy professionals. As well, pharmacy morale was inconsistently perceived by pharmacy professionals and varied depending on the type of pharmacy they worked in. Of the 6 domains

in the SAQ, working condition was scored the lowest by pharmacy professionals.

Implications: Although perception of safety culture in pharmacy practice is generally positive, the results of the SAQ show that there are still factors that generate discontentment from pharmacy professionals. Resolution of these barriers would contribute to a more robust safety culture within practice settings, and ultimately, improve the delivery of patient care.

Medication Incidents Associated with Patients with Renal Impairment: A Multi-Incident Analysis

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Background: Medication incidents associated with patients with renal impairment may result in increased exposure to medications, putting patients at risk of side effects, serious harm, or death. Healthcare professionals should learn from these incidents and adopt strategies to improve patient and medication safety.

Description: The objective of this multi-incident analysis was to gain a deeper understanding of the possible contributing factors to incidents associated with patients with renal impairment and to develop potential recommendations to prevent error recurrences.

Action: A total of 172 medication incidents associated with patients with renal impairment were extracted from a national incident reporting database from June 2014 to May 2019, with the subsequent performance of a qualitative and thematic analysis on 134 incidents that met the inclusion criteria.

Evaluation: Three main themes were identified from the multi-incident analysis, which included (1) recognition of renal impairment, (2) additional safeguards for patients with renal impairment, and (3) additional risks associated with renal impairment. Subthemes were further developed for each theme, which included (1a) assessment and availability of lab values, (1b) patient-related factors, (1c) medication-related factors, and (1d) documentation and computerization; (2a) accessibility to renal-specific care providers and (2b) special education provided to renal patients; and (3a) dialysis and (3b) drug therapy changes relating to renal function, respectively. Recommendations were offered for each corresponding theme identified from this analysis.

Implications: With an aging population at a higher risk of renal impairment, it is hoped that the findings from this analysis and the potential solutions presented can aid in the adoption of error reduction strategies and safe medication practices. Sharing lessons learned from medication incidents will contribute to overall safe and effective patient care.

Lessons Learned from a Multi-Incident Analysis on Medication Incidents Associated with Patient Harm in Saskatchewan

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Background: Medication incidents are preventable events, which may lead to patient harm, including adverse drug events, requirement of additional treatments, or critical events. By conducting a multi-incident analysis on reported harm incidents, system-based solutions can be developed to improve patient and medication safety.

Description: Multi-incident analysis is a qualitative methodology designed to derive common contributing elements amongst all reported incidents. Subsequently, potential recommendations to prevent incident reoccurrences can be developed. The objective of this multi-incident analysis was to gain a deeper understanding of the contributing factors to incidents associated with patient harm in Saskatchewan and to offer possible solutions.

Action: A total of 267 medication incidents associated with patient harm were extracted from a provincial incident reporting initiative from December 1st, 2017 to January 31st, 2019 and evaluated using a multi-incident analysis.

Evaluation: Four major themes were identified from the multi-incident analysis, which included (1) communication gaps, (2) non-traditional dispensing procedures, (3) order entry errors, and (4) product mix-up. Subthemes were further developed, which included (1a) patient communication, (1b) pharmacy staff communication, and (1c) interprofessional communication; (2a) compliance packaging and long-term care and (2b) high-risk procedures (e.g. methadone, compounding); (3a) technical errors and (3b) clinical errors; (4a) medication mix-up and (4b) patient mix-up, respectively. System-based recommendations were developed based on potential contributing factors identified for each sub-theme accordingly.

Implications: The thematic elements identified through the multi-incident analysis is applicable towards all medication-use practices. Sharing the findings of this analysis and the corresponding potential recommendations can aid with the adoption of error reduction strategies and promote safe medication practices. The importance of reporting, analyzing, and learning from past incidents should not be overlooked for continuous quality improvement in pharmacy practice.

Safety IQ: Lessons Learned from a Continuous Quality Improvement Program in Manitoba

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Background: Medication incidents involving patients are occurring and patient harm can be preventable. Twenty pharmacies in Manitoba participated in a standardized continuous quality improvement (CQI) program – Safety IQ – and retrospectively reported medication incidents to a national database anonymously.

Description: The objectives of this project were to apply a qualitative, multi-incident analysis approach to medication incidents that reached patients in Manitoba, to gain a better understanding of the contributing factors of these incidents, and to develop potential recommendations to prevent error recurrences.

Action: A total of 70 medication incidents involving patients were extracted from the Safety IQ provincial incident reporting initiative from July 2018 to June 2019 and a multi-incident analysis was conducted.

Evaluation: Four main themes were identified from the multi-incident analysis, which included 1) misidentification, 2) external discovery, 3) miscommunication, and 4) technology challenges. Subthemes were further developed for each theme (except for the last theme), which included (1a) patient misidentification, and (1b) product misidentification; (2a) patient/family/caregiver discovery and (2b) discovery by another healthcare professional; and lastly, (3a) miscommunication

between external healthcare professionals and pharmacy staff and (3b) miscommunication between patient and pharmacy staff. System-based recommendations were developed for each main them accordingly.

Implications: Confirmation of at least 2 patient identifiers by pharmacy staff will prevent unintentional mix-ups or misidentification of medications and patients. Using the "5 Questions To Ask About Your Medications" tool can help encourage and engage patient-healthcare professional dialogues. Findings from this analysis and potential recommendations presented would promote safe medication practices. Reporting, analyzing, and learning from anonymously reported medication incidents are critical for the success and ongoing engagement of pharmacy professionals in a provincial CQI initiative.

Intravenous Medication Safety – A Quantitative Analysis of Medication Incidents

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Background: Use of intravenous (IV) medications is ubiquitous in hospital practice. Awareness of the risk of medication-related harm is an important step towards system-level changes.

Objective: In order to determine future direction of medication safety, an analysis was conducted of IV medication incidents.

Methods: Using "drip", "IV", "intravenous", "infus*" as key search terms, the Individual Practitioner Reporting, Community Pharmacy Reporting, and Consumer Reporting databases from ISMP Canada's holdings and the National System for Incident Reporting database from the Canadian Institute for Health Information were queried for the period from October 2015 to September 2018. [National System for Incident Reporting, Canadian Institute for Health Information (October 18, 2018). Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed herein are those of the author, and not necessarily those of CIHI.]

Results: A total of 2210 reports related to IV medications were returned and total of 1583 reports were used for the quantitative analysis after screening and application of the exclusion criteria. For the table that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Conclusion: Of the top medications involved in harm reports, 3 are known high-alert medications. Their continued presence on this list highlights the need for additional safety strategies. The prominence of antimicrobials amongst the findings may be due to frequency of use but is deserving of further study.

Development, Dissemination and Evaluation of a "Direct Oral Anticoagulant Monitoring Tool" in Family Health Team Pharmacy Practice

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Background: Over the years, direct oral anticoagulants (DOACs) have quickly grown to favourable use over warfarin. However, regular monitoring is still imperative to ensure maximum safety and efficacy of these medications. Prior to this study, there was no standardized process for monitoring patients on DOACs in our hospital's family health team (FHT).

Description: The "DOAC Monitoring Tool" was developed and implemented at our hospital's FHT in an effort to facilitate the monitoring and documentation of patients on DOACs. The utility and acceptability of the tool was assessed thereafter.

Action: A monitoring form currently used in the hospital's outpatient pharmacy was adapted for use in the FHT setting based on input from literature and the FHT pharmacists. The tool was created as an electronic form compatible with Practice Solutions Suite, the electronic medical record used at the FHT. The tool was used whenever a pharmacist referral involved assessment of DOAC therapy. Proactive chart reviews of select high risk patients (individuals 80 years or older on a DOAC) were also conducted – however, this is not a regular task of the FHT pharmacists.

Evaluation: During the study period, 23 monitoring forms were completed. Three drug therapy problems were identified through the proactive chart reviews. The main barrier to uptake of the tool was the low number of requests made for DOAC-related pharmacy consults. Benefits of the tool include its ease of use and electronic accessibility. Limitations of the tool include its inability to highlight differentials between the therapeutic options and duplicate documentation in the patient chart.

Implications: Pharmacists can play a key role in the routine monitoring of DOACs and identification of drug therapy problems. Overall, the form was underutilized at our hospital's FHT. Piloting the form in other settings may provide additional information on the potential utility of the tool.

Optimizing the Management of Heart Failure: Diuretic Therapy at Discharge

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Background: Providing patients with diuretic instructions at discharge such as dose titrations based on weight is integral to heart failure management. There is currently no standardized approach at our centre for the provision and documentation of these instructions.

Objective: The goal was to characterize the management of patients admitted with heart failure to our institution, specifically focusing on what instructions are provided to them regarding diuretics at discharge.

Methods: The study was composed of a retrospective chart review of patients with a diagnosis of heart failure discharged June 1 to December 31, 2018 from our institution (General Internal Medicine and Cardiology units). An electronic survey was sent via email to 43 staff physicians on the GIM and Cardiology wards to better understand their perspective on diuretic instructions.

Results: The chart review included 84 patients. Most patients (96.4%) were discharged on a strong diuretic, mainly furosemide. Instructions regarding weight monitoring and diuretic titrations were provided to 25.9% and 14.8% of patients respectively. Many patients were advised to receive instructions from outpatient physicians; however, there were gaps in provision of follow-up instructions. Eighty percent of patients were advised to see their family physician, 54.8% to see a cardiologist, and 29.8% were referred to a heart failure clinic. Time to follow-up ranged from 1 to 6 weeks, and many patients were not given a recommended timeline. Only fifteen physicians completed the survey, and most mentioned that they provide diuretic instructions on discharge to heart failure patients. Some reasons for not providing instructions include lack of time and reliance on outpatient physicians to provide instructions.

Conclusion: Based on the chart review, most heart failure patients are discharged from our institution without receiving instructions on weighing themselves, adjusting their diuretics. More standardized approaches are needed for consistent provision and documentation of these instructions.

Roles and Perceptions of Pharmacists as Immunizers of Adult Patients in Tertiary Care Academic Hospitals: An Environmental Scan of Canadian Hospital Pharmacists

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Background: Vaccines are one of the most successful public health initiatives, yet adult vaccination rates remain low. Studies show hospitalization provides an opportunity to detect and address vaccination inadequacies; however, there is a lack of studies examining pharmacist vaccine advocacy roles in a hospital environment.

Objectives: The primary objective of this environmental scan was to identify the number of hospital pharmacists in Canada who self-identify as performing one of the following vaccine advocacy roles: educator, facilitator or administrator.

Methods: An electronic questionnaire, consisting of 52 pilot-tested questions, was distributed to pharmacists in tertiary care academic hospitals throughout Canada. The questionnaire was open for eight weeks and completed using the web-based Opinio™ software system. Closed-ended questions with specified response options were used to collect demographic data and personal practice information. The environmental scan was deemed to be a quality assurance project. Descriptive statistics were used to analyze data.

Results: Of the estimated 1967 hospital pharmacists in Canadian tertiary academic centers, 375 complete questionnaires were received, representing an estimated response rate of 19%. Most respondents, 87% (329/375) and 84% (315/375), reported engaging in at least one activity relating to education and facilitation, respectively. In contrast, only 41% (152/375) of respondents indicated they participate in at least one activity related to vaccine administration. Thirty-eight percent (142/375) of hospital pharmacists reported being currently certified to administer vaccines and only 13% (48/375) reported engaging in physical administration of vaccines. Nationally, 35% (131/375) of pharmacists were motivated to administer vaccines. The most common barrier reported was lack of time and the most common enabler was vaccine accessibility.

Conclusions: In Canada, most hospital pharmacists take on the roles of vaccine educators and facilitators. The vaccine administrator role is executed by hospital pharmacists less in comparison to the other vaccine advocacy roles.

Development of Geriatric Pharmacology Infographics (GPI): An Internet Survey among Health Care Professionals

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Background: Despite the increasing use of information design to deliver complex heath information, geriatric pharmacology information presented in visual form is a novel idea that may be efficient and effective. We created GPI prototypes (figure 1) with a clear hierarchy of important information and a systematic structure, using a graphic symbol system to better support clinical decision-making. We then evaluated them for further refinement.

Objective(s): To assess user-friendliness and overall reading experience of GPI, and to examine elements valued by clinicians to further refine the materials.

Methods: We recruited prescribers and pharmacists to elicit opinions about the prototypes through open-ended questions as part of a larger internet survey assessing efficacy and efficiency. We assessed appeal and user-friendliness, and used descriptive statistics to present results.

Results: Our survey had an 83.7% completion rate from 49 pharmacists, physicians, and nurse practitioners. Clinicians valued prescribing information (eg. adverse effects and monitoring parameters) but also visual elements, including organization and clarity of information. Conversely, additional elements, such as tapering and deprescribing recommendations would be helpful. Although many clinicians would make no changes to the GPIs, some felt that there was a learning curve for their use, and suggested the inclusion of a legend. 77.6% of respondents were satisfied with the overall appearance.

Conclusion(s): Geriatric pharmacology information design potentially conveys complex drug knowledge in a visually appealing way. We will further refine the GPIs to develop an innovative, scalable solution for use in medication optimization.

For the figure that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Closed System Transfer Device Sterility Testing to Validate Beyond-Use Date Extensions

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Background: The Cancer Care Ontario Beyond-Use Date Recommendations Report outlines guidance on utilizing closed system transfer devices (CSTDs) with single-dose vials to extend beyond-use dates (BUDs) from the current 6 hours to 7 days. This is provided that annual facility level sterility testing is completed.

Objectives: Sterility testing evaluates the ability of CSTD components to maintain vial sterility after multiple withdrawals. This sterility testing validates vial BUD extensions.

Methods: All procedures were completed in an ISO Class 5 biological safety cabinet. Ten 100 mL vials of tryptic soy broth were punctured using Equashield® vial adaptors and 5 mL of broth were transferred from one vial into another 100 mL broth vial on days 1, 4 and 8. The original 10 vials were stored at room temperature and the 30 subsequent vials were incubated at 35°C ± 2°C for 14 days. Vials were visually monitored for growth on days 1, 4, 8, 15 and 22. Following incubation, 0.5 mL of broth was plated on tryptic soy agar and 0.5 mL on sheep blood agar. Plating was completed to validate the absence of microbial growth. Plates were incubated for 14 days. Growth rates were expected to be equal or lesser than 1.8% as reported in previous literature. A negative control vial and 3 positive control vials (*S. epidermidis, Bacillus subtilis, Staphylococcus aureus*) were incubated for 14 days.

Results: No vials displayed visual signs of turbidity and 0% of plates demonstrated microbial growth. All 3 positive control vials displayed turbidity and the negative control vial remained clear.

Conclusions: CSTD components demonstrated the ability to maintain sterility in facility level testing, thus validating BUD extensions. Overall, BUD extensions offer cost savings through reductions in medication wastage and facility sterility testing ensures patient safety.

Lipid-Based Formulation of a Vaccine Adjuvant Enhances Mucosal Immunity

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Background: A triple adjuvant (TriAdj) comprised of innate defense regulator (IDR)-1002 peptide, poly(I:C), and polyphosphazene has shown promise for use in vaccines. A lipid-based formulation of TriAdj (L-TriAdj) was developed and assessed for mucosal and systemic immunological responses to intranasal vaccination.

Objective(s): To design and characterize a cationic lipid-based delivery system for nasal administration of TriAdj and determine its *in vivo* efficacy.

Methods: Lipidic cationic formulations (L-TriAdj) were characterized using particle sizing, zeta potential, mucin binding and electron microscopy. L-TriAdj with ovalbumin was administered intranasally to mice as a model vaccine. Control groups included saline, TriAdj without lipid, and antigen only. Serum and lymphocyte assays of IgG, IgA, IL-5 and TNF-α were performed to determine the systemic and mucosal immune response. ANOVA with Tukey's post hoc tests were performed and comparison was done on rank order-transformed data with the Kruskall-Wallis test and Tukey post hoc test ($p<0.05$).

Results: L-TriAdj formed a condensed cationic complex with a mean diameter of <200 nm. The most stable formulation (comprised of 50:50 mol:mol didodecyl dimethylammonium bromide and dioleoyl phosphatidylethanolamine) was chosen for *in vivo* assessment. Mice administered L-TriAdj vaccines intransally showed a significantly greater immune response than those administered vaccines with TriAdj alone, with no signs of toxicity. A balanced Th1/Th2 immune response demonstrated the superior systemic and mucosal immunity of the L-TriAdj formulation. Notably, IgA levels in serum were significantly greater in vaccinated mice receiving the lipid-based formulation.

Conclusion(s): The lipid formulation of TriAdj enhanced its mucosal and systemic efficacy following intranasal administration. The optimal formation of L-TriAdj generated the greatest immune response at the lowest antigen dose. This optimized formulation is currently being explored for several intranasal vaccines.

Clinical Pharmacy Key Performance Indicators and Pharmacist Job Satisfaction: A Mixed-Methods Study of Canadian Hospital Pharmacists

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Background: The clinical pharmacy Key Performance Indicators (cpKPIs) are a set of measures for quality improvement. Although they have links to important impacts on patient outcomes such as hospital readmissions, there is no data relating to their impact on Canadian hospital pharmacists' job satisfaction.

Objectives: To determine the level of job satisfaction among Canadian hospital pharmacists, and whether participation in the cpKPIs contributes to hospital pharmacist job satisfaction.

Methods: A mixed-methods study was conducted. An electronic survey was developed using a validated pharmacist job satisfaction tool and distributed nationally to hospital pharmacists between January 30 - March 14, 2019. Focus groups were conducted with pharmacists locally to further explore activities that contribute to their job satisfaction.

Results: Overall, 284 pharmacists from 9 provinces completed the electronic survey. The mean job satisfaction score among Canadian hospital pharmacists was 3.93 out of 5 (SD = 0.85). Job satisfaction scores increased as self-identified time spent performing the cpKPIs increased ($r = 0.148$, $p = 0.014$). Pharmacist satisfaction was found to increase with time spent performing medication reconciliation on admission ($\beta = 0.140$, $p = 0.032$) and decrease with time spent identifying and resolving drug therapy problems (DTPs) ($\beta = -0.153$, $p = 0.030$). However, pharmacists described the most reward on average from identifying and resolving DTPs in comparison to the other cpKPIs. As well, perceived reward from the identification and resolution of DTPs was found to have a positive association with job satisfaction ($\beta = 0.205$, $p = 0.013$). In focus group discussions, some cpKPIs were highlighted favourably, although pharmacists described some ambivalence towards patient education. The importance of having an impact, and receiving appreciation was highlighted.

Conclusions: Canadian hospital pharmacists are in general satisfied with their jobs, and participation in the cpKPIs was found to be positively associated with hospital pharmacist job satisfaction.

What Clinical Pharmacy Key Performance Indicators (cpKPI) Are Patients Receiving across Canada? A National cpKPI Patient Registry and Pooled Analysis

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Background: National consensus clinical pharmacy key performance indicators (cpKPIs) represent processes of care associated with an impact on meaningful patient outcomes. Hospitals across Canada have begun measuring and reporting cpKPI data on a local level, however, variations exist regarding which cpKPIs are measured and cpKPI practice profiles. Currently, a Canadian registry does not exist to capture cpKPI patient-level data and track pooled national progress.

Objective: To develop a national cpKPI patient registry and generate pooled national summary cpKPI reports to inform the advancement of pharmacy practice and improve patient outcomes.

Methods: In this national, quality improvement, observational study, volunteer hospitals measuring at least one cpKPI were enrolled and submitted aggregate cpKPI patient data for January - December 2018. Local hospital cpKPI data were summarized and pooled national reports were generated.

Results: In the inaugural year, 32 Canadian hospitals and 275,896 patients were enrolled. Of the 32 hospitals, 19 hospitals were acute care institutions, continuously measuring cpKPIs as patient proportions (core analysis). The most commonly delivered cpKPIs were Admission Medication Reconciliation, Pharmaceutical Care Plans, Drug Therapy Problems Resolved and Inter-professional Patient Rounds.

Conclusions: The first national registry for capturing cpKPI patient-level data in Canada was established. The results from this registry will facilitate identification of strengths, care gaps and opportunities for the provision of cpKPI-related processes of care across the country, permit hospital cpKPI profile benchmarking, cpKPI definition refinement, and support national best-practice sharing.

For the figure that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Implementation of Streamlined Electronic Workflow to Capture Key Performance Indicators (KPIs) for Pharmacists

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Background: Clinical Pharmacy Key Performance Indicators (cpKPIs) measure the quality of care provided by hospital pharmacists. Both workload documentation and chart documentation are required and important tasks of pharmacists however, it is a challenge to fit into the daily routine.

Description: Our goal was to implement the documentation of eight KPIs as defined by the CSHP Canadian cpKPI Collaborative and integrate the process within existing pharmacist workflows. A simplified workflow was created to include KPI documentation as part of the pharmacists' daily responsibilities, while maintaining workload collection.

Action: We embedded KPI documentation within the patient's electronic health record as it utilized existing workflows, simplified documentation, and is configurable to retrieve data for reporting. We assigned time values, based on practice leads consensus, to individual KPIs, thus removing the need to separately perform workload documentation. The new tool was rolled out after education on functionality and definitions of the various KPIs. Individual pharmacists received their own KPI data monthly as well as a satisfaction survey.

Evaluation: There were 22 pharmacists who responded to the survey. A majority (86%) of pharmacists documented KPIs on a daily basis. All respondents found the KPI process easy to use, and majority (90%) agreed the new process better enables task completion compared to previous methods. 64% of respondents agreed KPI data will assist with refining their own practice, and 77% agreed KPIs are an important reflection of their hospital practice.

Implications: Results suggest that the new process has simplified compliance to workload and KPI documentation, in addition to self-reflection of practice. In future, reports will be automatically generated and emailed to each pharmacist with monthly data.

Analysis of Pharmacist Clinical Documentation after CST Cerner Transformation

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Background: Lions Gate Hospital in Vancouver recently implemented Cerner, a new clinical information system replacing paper records. This switch changes how pharmacist's document, but having electronic records allows for easier workload statistics evaluation, and benchmarking of patient outcomes. Since Cerner implementation, pharmacist documentation has not been evaluated, so it is important to learn from their experiences before Cerner is implemented at other locations.

Description: The Canadian Society for Hospital Pharmacists have developed 8 clinical pharmacy key performance indicators (cpKPI). To use cpKPI's for benchmarking, there must first be a way to collect data and measure the cpKPI. Therefore, this project looked at both how current pharmacist documentation matches the cpKPI's, and whether the system allows for easy data collection and cpKPI measurement.

Action: General workload statistics were generated. Additionally, a sample of *pharmacist-notes* were mapped to cpKPI's. These notes were analyzed for how well the content matched to the note type and title, and it was assessed whether it was possible to map the notes based on the note type and title alone.

Evaluation: There were 7691 *intervention-notes* and 7667 *pharmacist-notes* created. It was not always clear how a *pharmacist-note* would map, due to non-descriptive titles and because most *pharmacist-note* types had variable content, mapping to 2-6 cpKPI's. Five of the 8 *pharmacist-note* types mapped fairly consistently, however the remaining 3 were the most frequently used and had the most variability and non-descriptive titles. For the table that goes with this abstract, please see Abstract Appendix, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/195/showToc

Implications: By evaluating strengths and weaknesses of pharmacist documentation in the current Cerner system, these results can be used to inform future use. Accurate cpKPI implementation allows for improvement in quality of care, and helps advance pharmacy practice.

Missing Dose Message Audit Using a Closed-Loop Health Information System - A Pharmacy Quality Improvement Project

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Background: Missing doses are a common time-consuming issue in hospitals. EPIC, an electronic health information system, has a secure InBasket messaging function that allows efficient exchange of messages between nurses and pharmacy technicians without using the phone. Missing dose messages are routed to a single InBasket for technicians to triage.

Description: The objectives were to observe the workflow of pharmacy technicians related to InBasket messaging and to identify the causes of missing doses submitted by nurses using the messaging function. The final step was to identify potential areas for improvement.

Action: A total of 80 missing dose messages were received from the ICU and Internal Medicine units over 4 days between the hours of 0600-1000. Potential causes for the missing doses were investigated and organized into 7 categories. The time taken per message by the technician was also recorded.

Evaluation: A number of missing doses were due to relocated and misplaced medications. In 18% of cases, nurses located the medication on the unit. In 25% of cases, the dispensed medication was not found on the unit. The remaining cases were either lost on patient transfer (16%), not yet prepared (15%), or confirmed as missing (6%). In 11% of cases, the message was incorrectly titled as missing, rather than refill required. Technicians spent less than 10 minutes resolving each message.

Implications: An electronic messaging function is an efficient communication tool between nursing and pharmacy, which allows re-ordering and documentation of missing doses. Recommendations include: 1) implementing pre-formatted phrases in the InBasket function to encourage consistent replies, 2) adding MAR notes to identify refrigerated medications, and 3) education on the appropriate labelling of the message. Potential causes of missing doses should continue to be evaluated for process improvement.

Discrepancies in "As Needed" Medications Prescribed during Hospitalization and at Discharge

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Background: Hospital discharges are an interface of care where patients are at high risk of medication discrepancies as they transition from the hospital to their home. Thus, discrepancies at discharge may result in significant consequences on the health care system due to the financial waste and increased potential for adverse patient outcomes.

Description: The objective was to review medication administration records and discharge medication reconciliation prescriptions to identify discrepancies. This included both PRN medications recently used in hospital and not ordered at discharge (potentially untreated condition) and PRN medications not recently used in hospital and ordered at discharge (potentially unindicated use).

Action: A randomized retrospective chart review including 76 patients was conducted in April 2019. Patients included were aged 18 years or older admitted to hospital longer than 7 days, had an electronic chart scanned, had PRN medication(s) prescribed during their hospitalization, and had a medication reconciliation form at discharge.

Evaluation: This study was able to identify and quantify discrepancies related to PRN medications at the interface between hospitalization and discharge. Seventy-nine per cent of patients (60/76) received at least one dose of PRN medication in the seven days before discharge. Twenty-nine percent of those patients (17/60) used PRN medications in the last 7 days of hospitalization but were not prescribed any at discharge. Twenty-one per cent of patients (16/76) did not have any doses of PRN medication in the 7 days before their discharge but 44% (7/16) of these were prescribed a PRN medication at discharge.

Implications: Reviewing the need for PRN medications on discharge is important for adequate management of patients' symptoms at home and to prevent potential unnecessary medication use. The current PRN medication administration record makes this review very time-consuming. New procedures should be considered to prevent polypharmacy and medication errors at discharge.

Investing in the Canadian Society of Hospital Pharmacists

Jody Ciufo

In my first year as the CEO of the Canadian Society of Hopital Pharmacists (CSHP), I have been grateful for the warm welcome I have received from members, our Board of Directors and branches across the country, and our staff team in Ottawa. This is especially important to me as a newcomer to both pharmacy and the healthcare sector. Drug shortages, pharmacare, excellence in practice, the opioid crisis, and other issues at the heart of patient care are all responses to some of the social challenges I've worked on throughout my career in national not-for-profit associations. Getting to work alongside pharmacy professionals whose primary concern is caring for the well-being of Canadians, especially for the frail and vulnerable among us, is an ongoing inspiration every day in this position.

The Board gave me a clear mandate to elevate the profile of hospital pharmacists, grow membership, engage the hospital pharmacy community, and amplify CSHP's collective voice. More importantly, they conveyed their clear commitment to fundamental change for the Society and willingness to fully collaborate to make this happen.

My predecessor, Myrella Roy, faced a significant challenge when she first became the Executive Director. With ingenuity and hard work, Dr Roy built a flourishing society over her 15 years at CSHP. During that time, the association world at large faced changes that have disrupted membership-based societies around the globe. The growth of niche associations, more competition for membership and sponsorship dollars, and the significant cutbacks in professional development by employers have challenged long-standing member organizations in virtually every sector. Within our world of hospital pharmacy practice, significant changes within the pharmaceutical industry have affected the nature of funding, relationships among industry, the healthcare sector, educational institutions, and, of course, professional associations. The business models under which CSHP flourished in the past are no longer enough to deliver the value that members expect and deserve.

To create the fundamental change required to operate in the new association world, the Executive Committee worked extensively with the Board, Branch Presidents, and affiliated boards to create a strategy to regain sustainability. Recent years have seen declining membership numbers and drops in revenues from a variety of sources. Looking down the road, we saw years of deficits ahead and felt we had a choice to make: either cut back on our services and programs for members to balance the budget or create a multi-year plan to invest in our Society to make sure we'd still be here to support the future of hospital pharmacy practice.

Of course, we chose to invest.

In a show of unanimous support, CSHP National, our Branches, and the affiliated boards agreed to contribute financially towards the common goal of becoming more member-driven, and offering more programs, services, educational opportunities, and relevance to today's generation of members, supporters, and students. Over 4 years, we will co-invest close to $1 million, with National contributing 85%, the Branches 12%, and the affiliated boards 3% to return to balanced budgets by 2023.

We're calling this a co-investment because of the collaborative way we worked together to find this path to sustainability. Over 4 months, the Board, the Branches, and the affiliated boards discussed several options at length and agreed upon this plan whereby Branches pay an amount according to a formula that balances their percentage of CSHP members and their ability to pay. We all agreed that it was fair, affordable, and, simply, the right thing to do.

The strategy will involve a large investment in human and technological infrastructure to allow us to deliver greater member value. The National Office now has a Marketing and Communications Department, led by seasoned Director Clara Wicke, to connect our community more closely and give voice to the

profession beyond our own membership. The office also has a larger pharmacy practice team under Christina Adams in the newly created position of Chief Pharmacy Officer. She and two Professional Practice Specialists will expand our programs and services and help our volunteer committees realize their goals. Overhauling our IT systems will give CSHP an edge in identifying and meeting the needs of diverse segments of the hospital pharmacy sector.

For the first time since 2013, CSHP conducted a comprehensive national survey of members to gather data about members' perceptions, beliefs, and preferences. The survey was designed to explore the propositions developed during the work on the Strategy Towards Sustainability: the big ideas of membership for pharmacy technicians, specialization, and a name change for the Society, as well as CSHP's value proposition and member priorities. At the same time, we conducted a separate survey with lapsed members to gain insight on why they left.

Almost 1 out of every 3 members took the 20-minute survey, a remarkably robust response rate, with 1012 respondents from our 3602 members. In addition, 9% or 515 respondents from the 5585 former members who gave up their memberships within the last 10 years cared enough to share their thoughts.

We needed to hear directly from our members why they belong to CSHP. The top 3 reasons were: "to belong to a professional association that represents high standards of practice", "to stay on top of news and developments in hospital pharmacy", and "to access information that makes me better at my job". Professional excellence underlines our *raison d'être*.

It should be no surprise, then, to learn that an overwhelming proportion of members (86%) described themselves as very or somewhat satisfied with the *Canadian Journal of Hospital Pharmacy* (*CJHP*), viewing it as a particularly valuable resource. Only the residency program scored higher, with a satisfaction level of 89%. Furthermore, the Journal is CSHP's best known product/service among members, with only 4% of respondents stating they were unfamiliar with the publication. Members value the high standards and quality that the *CJHP* Editorial Board and production team have insisted upon.

As part of the Strategy Towards Sustainability, CSHP committed to reporting regularly on targets for membership numbers, conference revenues, social media statistics, and other key indicators of success. To take place annually in the future, the national survey of members' views on programs, services, and the overall experience of belonging will be a critical measure in assessing progress and making adjustments along the way.

This past year has set the stage for CSHP's new beginnings as our 2015–2020 Strategic Plan comes to its natural end. The planning phase for 2020 and beyond is well underway, and this year will see the launch of our new Strategic Plan for 2020–2023.

The Strategy Towards Sustainability is our community's shared promise to ensure hospital pharmacy practice is always evolving into something better. I encourage you to recommit to our passionate community by stepping up to volunteer at the Branch or National level, participating in a CSHP conference, trying us out once again if you've let your membership lapse, or thinking critically about the knowledge explored in this issue of the *CJHP*. I'm genuinely honoured to be part of this community, and I look forward to the continued inspiration from the leadership and expertise of our volunteers and staff.

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

Investir dans la Société canadienne des pharmaciens d'hôpitaux

Jody Ciufo

Je suis très touchée de l'accueil chaleureux que m'ont réservé les membres de la Société canadienne des pharmaciens d'hôpitaux (SCPH), nos administrateurs et les filiales de partout au pays, mais aussi notre équipe à Ottawa tout au long de ma première année à titre de directrice générale de la SCPH. Une telle entrée en matière est particulièrement importante pour moi qui suis une nouvelle venue dans les secteurs de la pharmacie et des soins de santé. Les pénuries de médicaments, les programmes d'assurance-médicaments, l'excellence en matière de pratique, la crise des opioïdes et les autres enjeux au cœur des soins offerts aux patients sont des réponses à certains des défis sociaux sur lesquels je me suis penchée tout au long de ma carrière au sein d'associations nationales sans but lucratif. Pouvoir travailler avec les professionnels de la pharmacie dont la préoccupation principale consiste à veiller au bien-être des Canadiens, en particulier des plus faibles et des plus vulnérables d'entre nous, est une source d'inspiration au quotidien quand on se trouve dans cette position.

Le conseil m'a confié un mandat clair visant à valoriser l'image des pharmaciens d'hôpitaux, à augmenter le nombre d'adhérents, à susciter l'engagement de la communauté des pharmaciens d'hôpitaux et à amplifier la voix collective de la SCPH. Mais surtout, les membres du conseil m'ont communiqué leur ferme engagement à apporter des changements fondamentaux à la Société et ils m'ont assurée de leur pleine collaboration pour qu'ils se concrétisent.

Ma prédécesseure, Myrella Roy, a affronté un défi d'envergure lorsqu'elle est devenue directrice générale. Grâce à son ingéniosité et à son travail acharné, la Dre Roy a bâti une société florissante au cours des 15 ans qu'elle a passés à la tête de la SCPH. Pendant cette même période, l'ensemble du monde associatif s'est heurté à des changements qui ont bouleversé l'adhésion aux sociétés dans le monde entier. La croissance des associations de niche, la concurrence accrue visant à obtenir davantage de fonds des commandites et des adhésions ainsi que les compressions importantes dans le cadre professionnel effectuées par les employeurs ont remis en question les adhésions durables aux sociétés dans presque tous les secteurs. Dans notre secteur, des changements importants au sein de l'industrie pharmaceutique ont affecté la nature du financement et des relations entre les industries, le secteur des soins de santé, les établissements d'enseignement et, bien sûr, les associations professionnelles. Les modèles commerciaux qui ont favorisé l'épanouissement de la SCPH ne suffisent plus pour offrir à nos membres les avantages qu'ils méritent et auxquels ils s'attendent.

Afin d'effectuer le changement fondamental nécessaire à l'évolution du nouveau monde associatif, le comité exécutif a travaillé d'arrache-pied avec le conseil, les présidents des filiales ainsi que les conseils affiliés pour créer une stratégie visant à retrouver une croissance durable. Les dernières années ont été le témoin du déclin du nombre d'adhésions et des revenus de diverses sources. Nous avons entrevu des années de déficit à long terme et avons conclu qu'un choix s'imposait : réduire notre offre de programmes et services pour nos membres afin d'équilibrer le budget ou alors définir un plan pluriannuel visant à investir dans la Société pour faire en sorte qu'elle soit encore présente pour soutenir l'avenir de la pratique de la pharmacie d'hôpital.

Nous avons évidemment choisi d'investir.

Dans un élan de soutien unanime, le Bureau national de la SCPH, nos filiales et conseils affiliés ont accepté de contribuer financièrement à l'atteinte de l'objectif commun, qui consiste à être plus axé sur les membres, mais aussi à offrir plus de programmes, de services, d'occasions de formation et de pertinence à la génération actuelle des membres, des sympathisants et des étudiants. Au cours des quatre années à venir, nous investirons ensemble près d'un million de dollars pour retrouver notre équilibre budgétaire d'ici 2023 — le Bureau national contribuera à hauteur de 85 %, les filiales à hauteur de 12 % et les conseils affiliés à hauteur de 3 %.

Nous appelons cela un « co-investissement », terme qui reflète l'aspect collaboratif de notre travail visant à visant à assurer la durabilité. Pendant quatre mois, le conseil, les filiales et les conseils affiliés se sont penchés sur plusieurs options. Ils ont convenu de ce plan en vertu duquel les filiales paieraient un montant selon une formule calculée en fonction du pourcentage

d'adhérents à la SCPH et de leur capacité de payer. Nous avons tous convenu qu'il s'agissait là d'une manière équitable et abordable de procéder et que c'était ce qu'il y avait de mieux à faire.

La stratégie demandera un investissement important en infrastructure humaine et technologique pour que nous puissions fournir de plus grands avantages aux membres. Le Bureau national compte désormais un service de communications et de marketing dirigé par une directrice chevronnée, Clara Wicke. Il a pour mission de rapprocher les membres de notre communauté et de donner une voix à la profession bien au-delà de la seule adhésion. Le Bureau compte également une plus grande équipe de pratique en pharmacie, dirigée par Christina Adams, qui occupe le poste nouvellement créé d'agente principale en pharmacie. Elle s'associera à deux spécialistes de la pratique professionnelle pour élargir notre offre de programmes et de services et pour aider nos comités de bénévoles à atteindre leurs objectifs. La refonte de nos systèmes des technologies de l'information (T.I.) permettra à la SCPH de déterminer les besoins des divers segments du secteur de la pharmacie d'hôpital et d'y répondre.

Pour la première fois depuis 2013, la SCPH a mené une enquête nationale approfondie destinée à réunir des données sur la perception, les croyances et les préférences des membres. L'enquête a été conçue pour explorer les propositions développées pendant le travail portant sur la Stratégie de développement durable : les grandes idées en matière d'adhésion pour les techniciens en pharmacie, la spécialisation et le changement de nom de la Société ainsi que la proposition portant sur la valorisation de la SCPH et les priorités des membres. Nous avons mené simultanément une enquête distincte auprès des anciens membres pour comprendre les raisons de leur départ.

Près d'un membre sur trois a participé à l'enquête, qui prenait 20 minutes de leur temps. Il s'agit là d'un taux de réponse remarquablement élevé (1012 répondants sur nos 3602 membres). De plus, 9 % ou 515 répondants sur les 5585 anciens membres ayant renoncé à leur adhésion au cours des 10 dernières années ont souhaité faire part de leur opinion.

Nous devions entendre directement de la part de nos membres les raisons pour lesquelles ils adhéraient à la SCPH. Les trois raisons principales étaient les suivantes : « Appartenir à une association professionnelle qui représente des normes de pratique élevées », « Rester informé des nouvelles et des développements dans le domaine de la pharmacie d'hôpital » et « Accéder aux informations qui améliorent mon travail ». L'excellence professionnelle souligne notre raison d'être.

Il n'est donc pas surprenant d'apprendre qu'un nombre important de membres (86 %) se décrivent comme très satisfaits et plutôt satisfaits du *Journal canadien de la pharmacie d'hôpital* (JCPH) et le considèrent comme une ressource particulièrement précieuse. Seul le Programme de résidence a atteint un score plus élevé (avec un degré de satisfaction de 89 %). De plus, le *Journal* est le produit ou le service de la SCPH que les membres connaissent le mieux, puisque seuls 4 % disent ne pas le connaître. Les membres accordent une grande importance aux normes et à la qualité élevées sur lesquelles insistent le comité de rédaction et l'équipe de production.

Dans le cadre de sa Stratégie de développement durable, la SCPH s'est engagée à faire régulièrement le point sur le nombre d'adhérents, les revenus tirés des conférences, les statistiques relatives aux médias sociaux et les autres indicateurs clés de la performance. L'enquête nationale portant sur l'opinion des membres à l'égard des programmes, des services et de l'expérience générale d'adhésion, qui sera organisée chaque année, servira de mesure déterminante permettant d'évaluer les progrès et d'effectuer des ajustements en cours de route.

L'année dernière a permis d'ouvrir la voie à un nouveau départ de la SCPH, car le Plan stratégique de 2015-2020 touche à sa fin. La phase de planification pour l'année 2020 et les suivantes est en bonne voie, et cette année verra le lancement de notre nouveau plan stratégique de 2020-2023.

La Stratégie de développement durable constitue la promesse commune de notre communauté, qui se porte garante de l'évolution favorable de la pratique de la pharmacie hospitalière. Je vous encourage à vous réinvestir au sein de notre communauté dynamique en faisant du bénévolat à l'échelle de la filiale ou à l'échelle nationale, en participant à une conférence de la SCPH, en nous accordant une nouvelle chance si vous avez laissé expirer votre titre d'adhérent ou en réfléchissant avec un esprit critique aux thèmes abordés dans ce numéro du JCPH.

Je suis réellement honorée de faire partie de cette communauté et j'ai hâte de mettre à profit l'inspiration constamment nourrie par le leadership et l'expertise de nos bénévoles et des membres de notre personnel[o].

[Traduction par l'éditeur]

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

Épaulés par des géants

par Douglas Doucette

Ayant récemment clôturé mon année en tant que président de la Société canadienne des pharmaciens d'hôpitaux (SCPH), j'ai rejoint les rangs de dizaines d'autres présidents sortants de cette organisation. Pendant cette transition, j'ai réfléchi à la riche histoire de la Société et à son avenir prometteur à mesure de la mise en place de la Stratégie de développement durable (https://www. cshp.ca/strategy-towards-sustainability). Pour faire écho à George Bailey dans le film *It's a Wonderful Life*, je me suis demandé ce à quoi ressemblerait notre pratique si la SCPH n'existait pas!

La SCPH est le fruit de l'union de nombreuses associations régionales de pharmaciens d'hôpitaux. Elle a évolué pendant des dizaines d'années pour devenir l'association professionnelle nationale que nous connaissons aujourd'hui. Les valeurs et objectifs communs de nos membres nous unissent et nous permettent de bénéficier d'une communauté solidaire. Beaucoup de personnes qui m'ont motivé au cours de ma carrière ont été des chefs de file de la SCPH ainsi que des directeurs de pharmacie, des gestionnaires, des praticiens de première ligne, des résidents et des étudiants. Les membres de la SCPH ont été des pionniers par leurs réalisations individuelles et collectives. Sans une association nationale ayant soutenu nos efforts, notre profession n'aurait probablement pas occupé une place aussi importante au sein des institutions de la santé.

L'atout le plus important de la Société, ce sont ses membres : le cercle des pharmaciens, des résidents, étudiants et techniciens en pharmacie hospitalière, des cliniques, des environnements de soins primaires et à domicile, des universitaires et de l'industrie. Les membres sont soutenus par le conseil, le bureau national, les conseils affiliés, la fondation, les filiales et les comités qui participent tous à la réalisation de nos initiatives et travaillent de concert en vue de procurer des avantages à nos membres. Je suis reconnaissant de l'expertise des membres qui ont bâti la SCPH pour qu'elle fonctionne comme une association nationale efficace. Chaque filiale la raffermit en faisant rayonner nos valeurs communes au sein même de leur province et leurs dirigeants contribuent à la direction nationale du conseil, des comités, des groupes de travail et des RSP (Réseaux de spécialités pharmaceutiques). Nos membres sont le cœur et l'âme de la SCPH et ils soutiennent nos efforts d'un océan à l'autre.

Tout au long de son histoire, la SCPH a encouragé l'excellence et l'innovation en matière de soins aux patients. Malgré le fait que les pharmaciens auraient de toute façon atteint l'excellence sans association professionnelle, la SCPH a néanmoins permis qu'elle connaisse une diffusion et une adoption plus rapides, en favorisant le dialogue portant sur ce qu'elle est et devrait être. Les énoncés de position, les lignes directrices et les autres publications de la SCPH donnent une direction unique à la pratique de la pharmacie hospitalière d'un point de vue canadien. La SCPH de 2015 ou les initiatives en matière d'excellence en pharmacie hospitalière auraient-elles existé sans la SCPH? Tandis que des conférences et séminaires en pharmacie sont organisés dans toutes les régions du Canada, la SCPH continue de commanditer des rencontres dont la qualité du contenu est de niveau supérieur en y invitant des intervenants riches d'une expertise nationale et internationale. Les programmes de résidence sont accrédités par le Conseil canadien de résidence en pharmacie d'hôpital, ce qui facilite la définition des normes nationales et des formations avancées pour les jeunes leaders et cliniciens. Le *Journal canadien de la pharmacie hospitalière* est une publication respectée qui donne aux différents contributeurs l'occasion de communiquer leurs connaissances sur la manière de prodiguer des soins sécuritaires, efficaces et centrés sur le patient.

Certains lecteurs penseront que ce commentaire ne fait que décrire l'évidence même, mais il est d'autant plus justifié de réfléchir à ce qui fait de la SCPH une association professionnelle dynamique et pertinente. Comme George Bailey, ne tenons pas pour acquises nos précédentes réalisations. Nous avons une dette envers les personnes qui nous ont précédés et sur qui nous nous sommes appuyés pour faire progresser notre profession.

[Traduction par l'éditeur]

Douglas Doucette, B. Sc. (Pharm.), Pharm. D., FCSHP, est président sortant et agent de liaison interne de la Société canadienne des pharmaciens d'hôpitaux.

Standing on the Shoulders of Giants

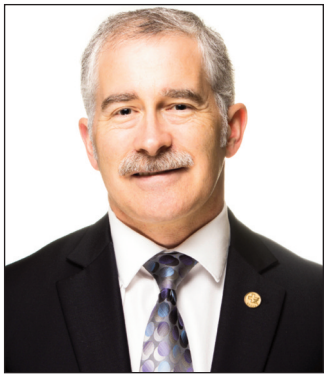
Douglas Doucette

Having recently completed my year as President of the Canadian Society of Hospital Pharmacists (CSHP), I joined dozens of others as a Past President of the organization. During this transition, I reflected on the Society's rich history and promising future as the Strategy Towards Sustainability is being implemented (https://www.cshp.ca/strategy-towards-sustainability). Mirroring George Bailey from the movie *It's a Wonderful Life*, I wondered what our practice would look like if CSHP did not exist!

CSHP was formed by the coming together of numerous regional associations of hospital pharmacists and has evolved over decades into today's national professional association. The shared values and goals of our members bind us together, giving us a community with common purpose. Many who have motivated me in my career have been leaders of CSHP, as well as pharmacy directors, managers, front-line practitioners, residents, and students. CSHP members have been trailblazers with their individual achievements and collective accomplishments. It is unlikely that our profession would be as prominent within healthcare institutions without a national association to support our efforts.

The Society's greatest asset is its members: the circle of pharmacists, residents, students, and pharmacy technicians from hospitals, clinics, primary and home care settings, academia, and industry. Members are supported by the Board, National Office, affiliated boards, Foundation, Branches, and committees—all of which support the execution of our initiatives and work to generate benefits for members. I am grateful for the expertise of members who have built CSHP to operate as an effective national association. Our Society is strengthened by all Branches as they project our shared values within their respective provinces and their leaders contribute to the national direction of the Board, committees, task forces, and PSNs (Pharmacy Specialty Networks). Our members are the heart and soul of CSHP, and they support our efforts from coast to coast to coast.

CSHP has fostered excellence and innovation in patient care throughout its history. While pharmacists would achieve practice excellence in the absence of a professional association, CSHP has enabled a more rapid spread and uptake, facilitating dialogue of what excellence is and should be. CSHP's position statements, guidelines, and other publications provide direction to hospital pharmacy practice with a unique Canadian perspective. Would CSHP 2015 or the Excellence in Hospital Pharmacy initiatives have existed without CSHP? While pharmacy conferences and seminars are organized in all regions of Canada, CSHP continues to sponsor events with high-calibre content and speakers of national and international expertise. Residency programs are accredited through the Canadian Pharmacy Residency Board, facilitating the development of national standards and advanced training for young leaders and clinicians. The *Canadian Journal of Hospital Pharmacy* is a respected publication providing authors with the opportunity to share their knowledge and work in pharmacy practice, adding to the body of knowledge on how best to provide safe and effective patient-centred care.



Some readers may think this commentary is stating the obvious, but that is all the more reason to reflect on what makes CSHP a relevant, dynamic professional association. Like George Bailey, let's not take for granted our past accomplishments. We owe a debt to those who have come before us and on whose shoulders we have stood in the advancement of our profession.

Douglas Doucette, BSc(Pharm), PharmD, FCSHP, is Past-President and External Liaison for the Canadian Society of Hospital Pharmacists.

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- favorisent la collaboration à des projets, à des recherches et à des programmes éducatifs pour répondre aux besoins des membres des RSP
- proposent des occasions supplémentaires aux membres d'agir à titre de leaders d'opinion et de ressources clés pour le Conseil de la SCPH sur des questions de pratique spécialisée, dont la rédaction de déclarations de principes, de lignes directrices et des documents d'information pertinents

La participation aux RSP est gratuite pour les membres de la SCPH.

Visitez **MY.CSHP.ca** et inscrivez-vous dès aujourd'hui!

Canadian Society of Hospital Pharmacists

Société canadienne des pharmaciens d'hôpitaux