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Pharmacy Leadership during the COVID-19 Pandemic

Peter J Zed

On March 11, 2020, the World Health Organization declared a pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an infection now known as coronavirus disease or COVID-19.[1] Since then, the world has undergone unprecedented disruption and change, and the impact on every aspect of our lives has been tremendous. The health care system in which we practise as pharmacists has been challenged to respond. Together with other health care providers, we have been called upon to provide swift and necessary leadership in response to the many rapidly changing issues that have emerged.[2] Leadership in pharmacy has been demonstrated in many ways during this pandemic, calling upon and highlighting our expertise, experience, capabilities, and resilience to do what is necessary in caring for our patients, ourselves, and our system. Although space does not permit a comprehensive survey, I would like to illuminate a few areas where our profession has tackled this pandemic through leadership in clinical care, collaboration, education and research, and communication.

As we prepared for what became the pandemic, planning for anticipated and uncertain impacts in our system has been a monumental challenge. Health and human resources planning has been front of mind for senior pharmacy administrators for months. The deployment or redeployment of staff and appropriate expertise has been critical, and many health authorities have developed flexible plans that are permitting our pharmacists and team members to provide clinical care to all patients. Attention to pandemic-specific clinical practice issues has been needed to ensure maintenance of the drug supply, especially medications that will be in greater demand during the pandemic. Planning for procurement of these essential medications, should demand outstrip supply, was essential. In addition, how medications are prepared, stored, and distributed at the system and institutional levels required careful consideration. The use of experimental therapies has also created challenges in clinical care. Drugs that have not undergone appropriate evaluation in relation to COVID-19 could have unintended consequences, including uncertainty about their efficacy and safety, as well as limiting access for patients who need them for previously approved indications.[3] It is indeed tempting to consider unproven therapies during a pandemic that is causing significant morbidity and mortality. However, the pandemic should not force us to choose between rapid, premature adoption of unproven therapies and adequate evidence to support efficacy and safety.[4] Finally, how we conduct clinical care has changed, the most striking difference being the move to virtual care, to keep both patients and health care team members safe. Regulatory bodies and provincial heath organizations have provided guidance and support in the provision of virtual care, and many practices outside the acute care environment have shifted entirely to virtual care.[5-7]

Collaboration on many levels has been required to manage this pandemic. The collaborations between public health organizations and the many stakeholders in health care have been obvious. In addition, there have been collaborations between organizations and stakeholders within our own profession, in a wide range of critical areas, including personal protective equipment (PPE), supply chain, regulation for safe dispensing and administration, clinical care, and health and human resources management. Some of these joint endeavours have resulted in appropriate advocacy for the drug supply, while others have focused on the availability of and education about proper use of PPE for pharmacy team members across the care continuum. Appropriate selection and use of medications, appropriate timing of doses and reduction in dosing frequency, and deprescribing of unnecessary medications are all areas where

pharmacy has worked in concert with other disciplines in providing leadership to preserve the drug supply, valuable PPE, and ultimately the safety of all members of the heath care team. I hope that after the crisis has passed, we will carry lessons from this collective leadership and collaboration into the post-pandemic era.

Throughout the pandemic, a staggering amount of information is being generated, and keeping up with the literature would be a challenge if not for the tremendous leadership of many in the field of pharmacy. This leadership was evident within the first week of the pandemic, when the BC Branch of the Canadian Society of Hospital Pharmacists (CSHP) launched a webinar series, led by experts in their respective areas, to share current best evidence on emerging pharmacotherapy issues.[8] The series has explored the use of nonsteroidal anti-inflammatory agents, renin-angiotensin-aldosterone blockers, hydroxychloroquine, corticosteroids, and statins, as well as providing education about transmission, testing, and COVID-19 considerations in special populations. Another webinar series, hosted by CSHP National, has provided further education for pharmacists and team members.[9] While nearly all prior clinical and pharmacy practice research activities have been suspended, research related to every aspect of COVID-19 has been encouraged and supported. This has created an opportunity for pharmacists to provide research leadership, by shifting valuable resources and expertise to participate in and lead projects in both clinical and pharmacy practice. Leadership in education and research has been welcomed and timely, and has supported the development and application of best evidence in these times of uncertain, conflicting, and rapidly changing information.

Perhaps the most important aspect of leadership observed in recent months has been our ability to communicate significant and rapidly changing information. Since the pandemic was declared, our public health officials have provided daily updates to the public and health care administrators and providers. This process has set the tone for varied and regular communication, through various modalities, from our provincial associations, regulatory bodies, volunteer professional organizations, and academic institutions.[9-12] For hospital pharmacists, the CSHP has been that voice and organizational leader, and I applaud the organization for its ability to mobilize its dedicated staff, volunteers, and expert members to ensure we have the information we need in this challenging time.

Leadership is always important, yet in recent years I have heard our profession question the future of leadership in pharmacy. It should not take a pandemic to propel our collective leadership into action, but I am proud of our profession and the shared leadership it has demonstrated recently. In particular, leaders at all levels within our profession should be commended for putting our patients and our people at the forefront. We will get through this together, and I am confident that the obstacles to be faced before this pandemic is over will be met with the same leadership we have shown to date. I challenge our profession to carry this momentum beyond the pandemic and—through our commitment, expertise, and dedication to excellence—to continue to lead, playing a critical role in our health care system and improving the heath outcomes of our patients.

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Le leadership en pharmacie pendant la pandémie de COVID-19

par Peter J Zed

Le 11 mars 2020, l'Organisation mondiale de la Santé déclarait un état de pandémie provoquée par le syndrome respiratoire aigu lié au coronavirus 2 (SARS-CoV-2), une infection désormais connue sous le nom de maladie à coronavirus, ou COVID-19[1]. Depuis, le monde a connu des perturbations et des changements sans précédent et l'impact sur tous les aspects de notre vie a été énorme. Le système de soins de santé au sein duquel nous exerçons en tant que pharmaciens a été obligé de réagir. Nous avons été appelés, avec les autres fournisseurs de soins de santé, à assurer un leadership rapide et nécessaire pour réagir à l'évolution rapide de situations problématiques[2]. Pendant cette pandémie, le leadership en pharmacie s'est illustré de nombreuses manières et a exigé de nous que nous fassions ce qui s'imposait pour nous occuper de nos patients, de nous-mêmes et de notre système, ce qui a mis en valeur notre expertise, notre expérience, nos capacités et notre résilience. Bien que l'espace ne se prête pas à une étude approfondie, je souhaite mettre en lumière ici quelques domaines où, durant cette pandémie, notre profession s'est illustrée par son leadership en matière de soins cliniques, de collaboration, d'éducation, de recherche et de communication.

Alors que nous nous préparions à ce qui allait devenir une pandémie, la planification des conséquences anticipées et incertaines sur notre système a été un défi monumental. La planification sanitaire et des ressources humaines était depuis des mois dans l'esprit de tous les gestionnaires en pharmacie. Le déploiement ou redéploiement des membres du personnel et des expertises adéquates a été un facteur essentiel, et de nombreuses autorités sanitaires ont élaboré des plans flexibles permettant à nos pharmaciens et membres de nos équipes de fournir des soins cliniques à tous les patients. Porter notre attention sur les problèmes cliniques pratiques, spécifiques à une pandémie, était nécessaire pour assurer l'approvisionnement en médicaments, particulièrement ceux faisant l'objet d'une demande accrue. La planification de l'approvisionnement en ces médicaments essentiels, si la demande devait dépasser l'offre, était primordiale. De plus, la manière de préparer, de stocker et de distribuer ces médicaments au niveau du système et des institutions exigeait une attention particulière. L'utilisation de thérapies expérimentales a également posé des défis en matière de soins cliniques. Les médicaments n'ayant pas fait l'objet d'une évaluation appropriée relativement à la COVID-19 pouvaient avoir des conséquences imprévues, y compris des conséquences incertaines concernant leur efficacité et leur innocuité, et limiter leur accès aux patients qui en avaient besoin pour des indications précédemment approuvées[3]. Il est en effet tentant d'envisager des thérapies sans fondement entraînant une morbidité et une mortalité importantes pendant une pandémie. Cependant, la pandémie ne devrait pas nous obliger à choisir entre l'adoption rapide et prématurée de thérapies sans fondement et des éléments de preuve adéquats pour étayer leur efficacité et leur sécurité[4]. Enfin, notre manière de prodiguer des soins cliniques a changé, la différence la plus frappante étant le passage des soins à un mode virtuel afin de préserver la sécurité à la fois des patients et des membres des équipes de soins. Les organismes de règlementation et les autorités sanitaires provinciales ont communiqué des directives sur l'offre de soins virtuels et l'ont encouragée, et de nombreuses pratiques extérieures à l'environnement des soins intensifs sont entièrement passées aux soins virtuels[5-7].

La collaboration à de nombreux niveaux a été nécessaire pour gérer cette pandémie. Les collaborations entre les organismes de santé publique et les nombreuses parties prenantes dans le domaine des soins de santé ont été évidentes. De plus, certaines ont vu le jour entre les organismes et les parties prenantes au sein de notre profession, et cela dans un large éventail de domaines cruciaux. On notera par exemple les domaines relatifs aux équipements de protection individuelle (EPI), à la chaîne d'approvisionnement, à la règlementation visant à délivrer et à administrer des médicaments de manière sécuritaire, aux soins cliniques et à la gestion des ressources humaines et de la santé. Certaines de ces initiatives communes ont résulté en un plaidoyer pertinent sur l'approvisionnement en médicaments, tandis que d'autres se sont focalisées sur la disponibilité des EPI et la sensibilisation à leur utilisation adéquate par les membres des équipes en pharmacie dans le continuum des soins. Le bon choix et la bonne utilisation des médicaments, la bonne synchronisation des doses et la réduction de leur fréquence ainsi que l'arrêt de la prescription des médicaments non essentiels sont des domaines où les services de pharmacie ont travaillé main dans la main avec d'autres disciplines en faisant preuve de leadership pour préserver l'approvisionnement en médicaments, les précieux EPI et, enfin, assurer la sécurité de tous les membres de l'équipe de soins. J'espère que lorsque la crise sera terminée,

nous tirerons des enseignements de ce leadership collectif et de cette collaboration.

Tout au long de la pandémie, une quantité impressionnante d'informations est produite, et rester au fait des publications aurait été un défi, si ce n'était du formidable leadership de beaucoup de professionnels du domaine de la pharmacie. Ce leadership a été évident au cours de la première semaine de la pandémie, lorsque la section de la C.-B. de la Société canadienne des pharmaciens d'hôpitaux (SCPH) a lancé une série de webinaires organisés par des experts dans leurs domaines respectifs, pour faire connaître les preuves actuelles les plus concluantes relatives aux problèmes de pharmacothérapie[8]. Cette série s'est penchée sur l'utilisation des agents anti-inflammatoires non stéroïdiens, les bloqueurs du système rénine-angiotensine-aldostérone, l'hydroxychloroquine, les corticostéroïdes et les statines; Elle a aussi permis de sensibiliser [nos membres] à la transmission, aux examens et aux considérations particulières de la COVID-19 dans des populations particulières. Une autre série de webinaires, organisée par le bureau national de la SCPH, a permis de sensibiliser davantage les pharmaciens et membres de l'équipe[9]. Malgré la suspension de près de la totalité des activités de recherche antérieures liées à la pratique clinique et en pharmacie, celles liées à tous les aspects de la COVID-19 ont été encouragées et soutenues, ce qui a donné aux pharmaciens l'occasion d'assumer un rôle de leadership dans la recherche, en transférant de précieuses ressources et leur expertise pour participer à des projets de premier plan dans la pratique clinique et en pharmacie. Le leadership en matière d'éducation et de recherche a été bien accueilli et opportun, il a permis de soutenir l'élaboration et l'application des meilleures pratiques en ces temps marqués par des informations incertaines, conflictuelles et en évolution rapide.

Au cours des derniers mois, l'un des aspects observés les plus importants a peut-être été notre capacité à communiquer d'importantes informations qui évoluaient rapidement. Depuis la déclaration de l'état de pandémie, nos autorités de santé publique ont quotidiennement informé le public ainsi que les administrateurs et fournisseurs de soins de santé. Ce processus a donné le ton aux communications régulières et variées de diverses instances, des associations provinciales aux organismes de règlementation, en passant par les organismes professionnels de bénévoles et les institutions universitaires[9-12]. Pour les pharmaciens d'hôpitaux, la SCPH a été cette voix et un leader organisationnel. Je salue la Société pour sa capacité à mobiliser son personnel dévoué, ses bénévoles et membres experts pour que nous disposions des informations nécessaires en ces temps difficiles.

Le leadership est toujours important pourtant, au cours des dernières années, j'ai entendu notre profession remettre en question l'avenir du leadership en pharmacie. Une pandémie ne devrait pas être nécessaire pour pousser notre leadership collectif à agir, mais je suis fier de notre profession et du leadership commun dont il a récemment fait preuve. En particulier, des leaders à tous les échelons de notre profession qui doivent être salués pour avoir mis nos patients et notre personnel à l'avant-garde. Nous traverserons ensemble cette situation et j'ai confiance que les obstacles auxquels nous serons confrontés avant que cette pandémie ne prenne fin seront abordés avec le même leadership que nous avons démontré jusqu'à présent. Je mets au défi notre profession de continuer sur son élan au-delà de la pandémie et, grâce à notre engagement, à notre expertise et à notre dévouement pour atteindre l'excellence, de continuer à être le fer de lance en jouant un rôle déterminant dans notre système de santé et en améliorant les résultats cliniques de nos patients.

[Traduction par l'éditeur]

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Barriers to and Enablers of Implementation of High-Value Interventions by Renal Pharmacists: A Qualitative Study Informed by the Theoretical Domains Framework

William Nevers, Alice Ratcheva, Kate Boutin, Sean K Gorman, Richard Slavik, and Natalie Lesko

ABSTRACT

Background: Previous studies have shown that patients with chronic kidney disease who are followed by a renal clinical pharmacist have improved clinical outcomes. In 2016, a consensus list of quality indicator drug therapy problems (QI-DTPs) was developed by renal clinical pharmacists to help prioritize which renal patients should receive interventions. Before QI-DTP interventions can be implemented in clinical practice, barriers to and enablers of their use need to be identified, to allow development of strategies to overcome the barriers and apply the enablers.

Objective: To identify modifiable barriers to and enablers of implementation of renal QI-DTP interventions by renal clinical pharmacists.

Methods: In this exploratory qualitative descriptive study, one-on-one, semistructured, audio-recorded telephone interviews were conducted with renal clinical pharmacists to identify the barriers to and enablers of implementation of renal QI-DTP interventions. The interviews consisted of questions developed according to the Theoretical Domains Framework.

Results: Interviews were conducted with 13 renal pharmacists from across Canada. The main barriers to implementation of renal QI-DTP interventions that participants identified were knowledge gaps, prioritization, and nephrologist acceptance. The main enablers identified were training, colleague support, and better patient care.

Conclusion: Three barriers to and three enablers of implementation of renal QI-DTP interventions were identified. These barriers and enablers can be used to help with pharmacist education and to optimize the care that pharmacists provide to renal patients.

Keywords: quality indicator drug therapy problems, barrier, enabler, renal pharmacist, behaviour change

RÉSUMÉ

Contexte : Des études précédentes démontrent une amélioration des résultats cliniques de patients souffrant d'une maladie rénale chronique, qui sont suivis par un pharmacien clinicien en néphrologie. En 2016, des pharmaciens cliniciens en néphrologie ont mis au point une liste consensuelle des indicateurs de qualité des problèmes de pharmacothérapie (QI-DTP) pour les aider à prioriser les patients souffrant d'une insuffisance rénale, qui doivent subir une intervention. Avant de mettre en place ces QI-DTP en pratique clinique, on doit déterminer les éléments qui entravent et facilitent leur utilisation pour pouvoir élaborer des stratégies visant à surmonter les obstacles et à appliquer les éléments facilitateurs.

Objectif : Déterminer les éléments modifiables qui entravent et facilitent la mise en place des QI-DTP par les pharmaciens cliniciens en néphrologie lors d'interventions rénales.

Méthodes : Dans cette étude exploratoire, descriptive et qualitative, des entretiens téléphoniques individuels, semi-structurés et enregistrés ont été menés auprès de pharmaciens cliniciens en néphrologie pour déterminer les éléments qui entravent et facilitent la mise en place de QI-DTP lors d'interventions rénales. Les entretiens consistaient en des questions préparées selon le *Theoretical Domains Framework*.

Résultats : Les entretiens ont été menés auprès de 13 pharmaciens en néphrologie de partout au Canada. Les principaux éléments entravant la mise en place de QI-DTP lors d'interventions rénales déterminées par les participants étaient : le manque de connaissances, la priorisation et l'acception des néphrologues. Les principaux éléments facilitant la tâche étaient : la formation, le soutien des collègues et de meilleurs soins offerts aux patients.

Conclusion : Trois éléments entravant et trois éléments facilitant la mise en place de QI-DTP lors d'interventions rénales ont été déterminés. Ils peuvent être utilisés pour contribuer à la formation du pharmacien et pour optimiser les soins offerts aux patients qui souffrent d'insuffisance rénale.

Mots-clés : indicateur de la qualité des problèmes de pharmacothérapie, obstacle, facilitateur, pharmacien néphrologue, changement de comportement

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INTRODUCTION

The number of individuals with chronic kidney disease (CKD) in Canada is about 2.4 million, and about one-third of these have stage 3 to 5 CKD.[1] On average, patients receiving hemodialysis take 10 to 12 medications per day, putting them at high risk of experiencing drug therapy problems (DTPs).[2] A DTP is any undesirable event or risk experienced by the patient that involves drug therapy and prevents the patient from achieving the goals of therapy.[3] Renal clinical pharmacists collaborate with other health care professionals on multidisciplinary teams to help prevent and resolve DTPs.[4,5] Patients with CKD who receive care from a health care team that includes a renal clinical pharmacist experience reduced mortality, fewer hospital admissions, improved medication adherence, and fewer adverse effects from medications.[5]

However, the ratio of renal clinical pharmacists to patients who have CKD or need dialysis varies across Canada, and there are no consensus guidelines that recommend an appropriate ratio of pharmacists to patients in the renal care setting.[6] This means that renal pharmacists may not have the capacity to identify and resolve all DTPs in all renal patients. As a result, in order to provide the most value to patients and the health care system, renal clinical pharmacists need to prioritize which patients they see and which of these patients will receive high-value interventions, that is, interventions most likely to improve patients' health outcomes.[7,8]

In 2016, a consensus list of quality indicator drug therapy problems (QI-DTPs) was developed by a group of renal clinical pharmacists to help renal pharmacists prioritize the patients who should receive direct patient care.[9] Each QI-DTP intervention was developed by extracting strong recommendations from renal clinical practice guidelines published between 2010 and 2015 and identifying those that met the following criteria: is based on a prevalent and impactful complication of CKD, is supported by high-quality evidence (randomized controlled trial or meta-analysis), results in resolution of a DTP, and improves the quality of drug therapy. All candidate QI-DTP interventions meeting these criteria were reviewed by 18 Canadian renal clinical pharmacists, who used a Delphi process to reach consensus on which QI-DTP interventions would result in advancement of renal pharmacy practice and improve the quality of patient care. This process resulted in 17 consensus-based renal pharmacy QI-DTP interventions that renal clinical pharmacists could use to assist in prioritizing the patients to whom they provide care and the interventions they deliver.[9]

The presence of QI-DTPs does not guarantee that pharmacists will implement the associated interventions in their practice. Published research has demonstrated that knowledge does not directly translate into behaviour and practice change; this discrepancy can be described as the know–do gap.[10,11] Pharmacists do not always implement evidence-based best pharmacotherapy practices for various reasons, such as clinician-, patient-, and system-related factors.[8,11-15] More specific to renal pharmacy, some renal pharmacists are not aware of evidence-based guidelines for clinical practice.[16] It is essential to close the know–do gap with respect to renal QI-DTPs, to ensure that patients with renal disease who have prevalent and impactful drug therapy needs receive high-quality pharmaceutical care. There has been some research on the interventions that renal pharmacists should perform, but there are few high-quality studies that address the effects of such interventions in renal patients.[17] A systematic review published in 2012 suggested that medication reviews, patient education, promotion of compliance, and protocol development would benefit renal patients and the renal care team, and would also confer cost savings.[18] Barriers to the implementation of these interventions were lack of funding; lack of hospital administrator's approval; staff shortages; lack of academic training; relationships with physicians; and attitudes of pharmacists, patients, and the renal health care team.[18] Enablers identified were access to information sources, consent from the care team, access to patient profiles, and having a full-time renal pharmacist on the team.[18] The current study focuses on identifying specific barriers and enablers to implementing the 17 renal QI-DTP interventions that were systematically identified in the previous study.[9]

The design of implementation interventions aimed at closing the know–do gap requires a systematic approach that is both transparent and rooted in a validated theoretical framework.[19] The Theoretical Domains Framework (TDF) is an evidence-based tool that can be used to identify barriers to and enablers of behaviour change in clinical practice.[13,20] This validated tool was developed to identify psychological and organizational theory associated with health care providers' clinical behaviour change.[13,20] The TDF consists of 14 domains covering the main factors that influence behaviour, specifically social influences, social and professional role and identity, knowledge, environmental context and resources, beliefs about capabilities, behavioural regulation, beliefs about consequences, skills, memory attention and decision processes, intentions, optimism, goals, emotion, and reinforcement.[13,20]

According to the TDF, there are 4 steps to developing a theory-informed implementation intervention: identifying the problem (who needs to do what activity differently), assessing the problems (finding barriers and enablers), developing possible solutions (which interventions could overcome the barriers and promote the enablers), and evaluating the intervention (measuring and understanding the behaviour change).[13]

The TDF approach to designing behaviour change interventions has been integrated into the Behavivour Change Wheel. The Behaviour Change Wheel is a tool that describes the behaviour of interest in terms of sources of capability, opportunity, and motivation (COM-B). According to the COM-B system, an individual must possess capability, motivation, and opportunity in order for behaviour change to occur.[12] The 14 domains of the

TDF have been independently mapped onto the COM-B segments. This is helpful for the design of future behaviour change interventions, because each source of behaviour outlined in the COM-B system has been linked to proven behaviour change interventions. Therefore, if barriers and enablers for a target behaviour are assessed using the TDF, they can be mapped to the COM-B system, which can then be used to select suitable behaviour change interventions to attempt to systematically change the behaviour.

The aim of this study was to identify barriers and enablers to implementing the renal QI-DTP interventions, as perceived by renal clinical pharmacists. The results of this study will inform future development and implementation of behaviour change interventions directed toward renal QI-DTPs, which will help to standardize practice and improve renal patient care.

METHODS

Study Design, Sampling, and Setting

This exploratory qualitative descriptive study was conducted by means of one-on-one, semistructured, audio-recorded telephone interviews with renal pharmacists. A convenience sample of renal pharmacists from across Canada was sought, including professionals from different provinces, with different levels of experience, working in a variety of practice settings. Potential participants were included if they were clinical pharmacists working in various renal settings (chronic kidney disease, hemodialysis, peritoneal dialysis) at tertiary, regional, or community hospitals across Canada. The specific inclusion criterion was spending more than 50% of their time providing direct patient care to adults with CKD, with or without dialysis. Pharmacists who served as panelists in the study for developing renal QI-DTPs, participants who were unable to complete the interview before April 1, 2017, and those unable to communicate in English were excluded. Participants were recruited by the principal investigator (W.N.) using the Renal Pharmacist Network listserv (www.renalpharmacists.net). A brief message was posted to the listserv, inviting interested pharmacists to contact the principal investigator by email, supplying their phone number. All renal pharmacists who responded and met the inclusion criteria were included in the study, and an interview time was scheduled according to their availability. All participants provided written informed consent (signed consent forms sent by e-mail to the principal investigator). This study was approved by the Interior Health Authority Research Ethics Board. The study interviews were conducted between February 13 and February 28, 2017. Participants did not receive any compensation.

Semistructured Interview Guide

The interview guide used questions adapted from the 14 domains of the TDF to identify factors that influence behaviour change (see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/198/showToc).[21,22] The interview guide was developed by 2 of the investigators (W.N., S.K.G.), and was then reviewed and edited as necessary by the other investigators, to improve the clarity and quality of the interview questions. These questions were open-ended and aimed to determine the factors affecting whether renal pharmacists would address renal QI-DTPs in their daily practice. There were 1 or 2 questions for each TDF domain, and follow-up prompts were included as needed to account for certain constructs of the TDF. The intention was to keep the interviews relatively short (20–30 min), so it was not possible to ask a series of specific questions for each QI-DTP. Instead, the questions were broad and encompassed all 17 of the renal QI-DTP interventions as a group, analogous to a group of recommendations from a clinical practice guideline. Demographic information was collected before each interview began. To minimize bias, all potential participants were asked whether they had any known or perceived conflicts of interest related to any of the renal QI-DTPs interventions; anyone who declared the existence of such a conflict of interest was excluded.

Participant Orientation to Renal QI-DTP Interventions

Three weeks before the interview, a 10-min slide presentation with voice-over was sent by e-mail to each participant, to provide background on the renal QI-DTP interventions, the purpose of the study, the study methods, and the interview process. Participants also received an electronic copy of the list of renal QI-DTP interventions. Participants were asked to confirm by e-mail that they had viewed the slide presentation. During this 3-week timeframe and throughout the study period, the principal investigator was available to answer questions from participants related to the research process.

Data Collection

All of the telephone interviews were conducted by a trained investigator (A.R.). The interviews were audio-recorded and transcribed verbatim.

Data Analysis

The audio-recorded interviews were anonymously transcribed and coded by the same investigator who conducted the interviews (A.R.) using NVivo 11 Starter for Windows software (QSR International Americas Ltd, Burlington, Massachusetts), and reflexive journaling was used to lend rigour and trustworthiness to the data. Two of the interviews were coded by a second investigator (W.N.) to check inter-rater reliability. The data were analyzed through a directed content analysis using the TDF.[23] A coding guide adapted from previous literature was used to enable thematic and directed content analysis of participants' responses.[22] The coding guide (Appendix 2, available at

https://www.cjhp-online.ca/index.php/cjhp/issue/view/198/showToc) was agreed upon by members of the research team to ensure consistent coding. Codes reflected the 14 TDF domains (as listed above) and were categorized into themes to determine modifiable barriers and enablers to implementing the renal QI-DTP interventions into practice, as identified by the participants. Each participant response or applicable portion of a response was coded to the most appropriate of the 14 TDF domains. The total number of times each TDF domain was matched to a participant response was captured. Direct quotes supporting the themes were extracted to strengthen the trustworthiness of the analysis. The responses corresponding to the TDF domains for knowledge, behavioural regulation, skills, and memory attention and decision processes were mapped to "capability" on the COM-B. The responses corresponding to the TDF domains for social influences and environmental context and resources were mapped to "opportunity", and the responses corresponding to the TDF domains for social and professional role and identity, beliefs about capabilities, beliefs about consequences, intentions, optimism, and goals were mapped to "motivation".

The investigator who performed the majority of the coding wrote in a reflexive journal, after coding each interview, to document thoughts about participants, questions, and responses.

RESULTS

Thirteen renal pharmacists from 6 Canadian provinces participated in this study, and all participants completed the full interview. The interview duration ranged from 19 to 34 min. Relevant participant characteristics are reported in Table 1. Of note, most participants were female (9/13), the group was about evenly divided in terms of experience as a renal pharmacist (with about one-third in each of the 3 categories, for 1–5 years, 6–10 years, and 11 or more years of experience) and more than half (7/13) had completed a pharmacy practice residency or a post–entry-to-practice doctor of pharmacy degree.

Twelve TDF domains were coded from the interviews; the emotion and reinforcement domains were not reflected by comments during the interviews and therefore were not coded. A total of 349 utterances were coded across these 12 TDF domains (Table 2). The 2 most frequently coded TDF domains were social influences (87 utterances) and environmental context and resources (53 utterances), whereas the 2 least frequently coded TDF domains (excluding the 2 domains with no coding) were optimism (3 utterances) and goals (1 utterance). Sample utterances for each domain are shown in Table 3.

Barriers to Implementation of Renal QI-DTP Interventions

Three themes were identified that reflected barriers to renal pharmacists' implementation of renal QI-DTP interventions (Table 4). The themes for barriers reflected all 3 components of the COM-B system (capability, opportunity, and motivation).

From a capability perspective, some participants did not feel that they had sufficient knowledge of the renal QI-DTPs to perform high-priority interventions. For example, one participant stated, "When it comes to initiating intravenous iron therapy, I would probably like a little bit more training. I mean, I know the basics but I haven't actually initiated IV iron therapy on any pre-dialysis patients. It is done, but I think it's more commonly done in hemodialysis patients. I don't have experience with that" (Pharmacist 5).

Table 1. Participant Characteristics

Characteristic	No. (%) of Participants *n* = 13
Sex, female	9 (69)
Province of practice	
British Columbia	1 (8)
Alberta	2 (15)
Manitoba	3 (23)
Ontario	5 (38)
Quebec	1 (8)
Nova Scotia	1 (8)
Experience as a renal pharmacist	
1–5 years	5 (38)
6–10 years	4 (31)
≥ 11 years	4 (31)
Highest academic credential	
Bachelor of Science in Pharmacy	6 (46)
Pharmacy Residency	3 (23)
Post entry-to-practice PharmD	4 (31)
Patient subpopulation*	
CKD, all stages pre-dialysis	7 (54)
ESRD, hemodialysis	9 (69)
ESRD, peritoneal dialysis	3 (23)

CKD = chronic kidney disease, ESRD = end-stage renal disease.
*The percentages sum to more than 100 because some respondents were involved with care for more than 1 patient subpopulation.

Table 2. TDF Domains and Utterances

TDF Domain Code	No. of Utterances
Social influences	87
Environmental context and resources	53
Beliefs about capabilities	37
Beliefs about consequences	37
Social/professional role and identity	36
Behavioural regulation	26
Skills	23
Knowledge	20
Intentions	13
Memory attention and decision processes	13
Optimism	3
Goals	1
Emotion	0
Reinforcement	0
Total utterances	349

TDF = Theoretical Domains Framework.

Table 3 (Part 1 of 2). Participants' Direct Quotations

TDF Domain Code	No. of Participants*	Barrier	Enabler
Social influences	13	I work with about 13 different nephrologists and they all seem to do their own thing. So these are excellent guidelines and it was great to learn how rigorously they were came up with ... but having said that, as a pharmacist, we make a recommendation and then the nephrologist sometimes decides to do their own thing anyway. (Pharmacist 5)	I suppose a lot of it has to do with your communication with your nephrology team. Over the years you get comfortable with the people working on your team ... the nurses, nephrologist, etc. I think part of being able to do all of these interventions is having a trust and a comfort level with the team that you work with. (Pharmacist 3)
Social and professional role and identity	13	The biggest barrier is our role in the clinic. It's primarily nephrologist driven. So while we're there to provide recommendations, it all goes to the nephrologist and the nephrologist determines what changes are made primarily ... in this particular location. (Pharmacist 5)	I think it's our role to actually identify areas where you would implement the QI ... to communicate to the other health care providers working with us what we would want to implement and why. (Pharmacist 1)
Knowledge	13	Well definitely I would have to brush up on my knowledge of antihypertensive treatment in renal patients, especially the ones who are not yet on dialysis. I just find that there's a lot of background that I don't know and I just don't know where to start. (Pharmacist 2)	I think education is also an important one. So you have to have confidence when you want to make recommendations, and if you are making recommendations, you really need to be able to back it up with as much evidence as you can ... and so having the continuing education, knowing about the studies that have been done in the area, or the practice guidelines, that sort of thing. What'll help you to feel more confident when you're making the recommendations to other folks on the teams, I think that's an important part as well. (Pharmacist 3)
Environmental context and resources	13	Main barriers are again time constraint, to nephrologist availability. I mean you can text it, but sometimes it's easier to discuss it fully because the nephrologist may not have all the information in front of them. That would probably be the 2 main barriers. I mean other barriers ... I do have some responsibilities with the central pharmacy. (Pharmacist 9)	Yeah, I think human resources is certainly one, just literally having enough people to be able to review all the medical conditions ... see where there are issues, drug therapy issues ... and then be able to resolve them. (Pharmacist 3)
Beliefs about capabilities	13	I would say I'm barely confident. Definitely there's room for improvement in my confidence level. If I had to attach a number to it, I would say 70% ... 75%. (Pharmacist 4)	I'm fortunate in that it's not ... to integrate into my practice at all ... just because I'm dedicated to the hemodialysis, 100% clinical ... so I mean for me these quality indicators would not be ... none of them would be difficult for me to initiate. (Pharmacist 1)
Behavioural regulation	13	We have management algorithms for anemia management ... so it's primarily nursing driven. (Pharmacist 8)	We have some policies and procedures ... a lot of guidelines set up in place, we have them through the South Alberta Renal Program. They have lots of built-in policies on that kind of stuff. So they have a statin policy, they have a blood pressure policy, Aspirin [acetylsalicylic acid] and those types of preventative things. (Pharmacist 5)
Beliefs about consequences	12	I'm not sure that there is really a downside, but I wonder if I were doing all these things, that other things would be pushed aside and maybe I would be focusing on these and not seeing the patients as a whole ... Maybe it would take away some of that holistic approach. (Pharmacist 2)	Oh, just job satisfaction. Feeling like we are actually ... affecting outcome. I think that's a big one. And not just kind of going through the motions. I think that maintaining your competence and your confidence helps a lot towards being happy with your job (Pharmacist 4).
Skills	11	When it comes to initiating intravenous iron therapy, I would probably like a little bit more training. I mean, I know the basics but I haven't actually initiated IV iron therapy on any pre-dialysis patients. It is done, but I think it's more commonly done in hemodialysis patients. I don't have experience with that. (Pharmacist 5)	I stepped away and went to school for a couple years just so that I could develop these skills. I'm pretty comfortable implementing these QIs and again lucky that I have the support of the nephrology team so I can actually make changes. (Pharmacist 9)

continued on page 182

Table 3 (Part 2 of 2). Participants' Direct Quotations

TDF Domain Code	No. of Participants*	Barrier	Enabler
Memory attention and decision processes	11	NA	I think it's on the monthly bloodwork, especially in hemodialysis. Any time we are off target for one of these QI-DTPs an intervention would be welcome. It's a shared intervention I guess, with the nephrologist ... but in this particular set-up here, since the nephrologists aren't always there our place as a leader in drug therapy interventions are absolutely great to have. (Pharmacist 7)
Intentions	10	Well, things like pharmacokinetic monitoring and things that have to be done on that day at that time would be higher priority and these would be sort of, nice to improve if possible. Might influence outcomes long term. (Pharmacist 2)	Well, when I'm in clinics, which is probably 70% of the week, they are high priority, as the pharmacist on the team. But when I'm not in clinics, I'm not usually dealing with that, I'm just preparing ... so I guess medium. (Pharmacist 5)
Optimism	3	Because when you talk about what applies to a dialysis population then for sure, the way funding is changing in Ontario right now ... in the immediate pre-dialysis to dialysis population, I'm not sure some of these interventions are relevant. (Pharmacist 6)	I agree that it's possible to integrate all of them. In terms of accomplishing some of these changes, it might take months. (Pharmacist 10)
Goals	1	NA	Yeah we have a bone mineral, anemia, med rec, etc. ... each has its own quality team within the nephrology program. So within each quality team, there are different projects with priority so a lot of ... not all, but some of my focus for my work is dictated by achieving the goals of the program, and how I can help achieve those goals. (Pharmacist 8)
Emotion	0	NA	NA
Reinforcement	0	NA	NA

DTP = drug therapy problem, NA = not applicable, QI = quality improvement, TDF = Theoretical Domains Framework.
*The number of participants who mentioned the particular TDF domain code.

Table 4. Barrier Themes*

Category	Theme
Capability	Renal pharmacists do not feel they have sufficient knowledge to perform high-priority interventions.
Opportunity	Renal pharmacists are limited in their ability to perform high-priority interventions by the nephrologists with whom they work.
Motivation	Renal pharmacists do not consider the renal QI-DTP interventions to be the highest-priority interventions.

QI-DTP = quality indicator drug therapy problem.
*Based on the Behaviour Change Wheel, a tool that describes the behaviour of interest in terms of sources of capability, opportunity, and motivation (COM-B). According to the COM-B system, an individual must possess capability, motivation, and opportunity in order for behaviour change to occur.[12]

The renal pharmacists who participated in this study did not consider the renal QI-DTP interventions to be the highest-priority interventions, which may underlie a motivation deficit pertaining to performing drug therapy interventions that have been proven to improve outcomes in these patients. For example, one participant stated, "Well, things like pharmacokinetic monitoring and things that have to be done on that day at that time would be higher priority and these would be sort of, nice to improve if possible. Might influence outcomes long term" (Pharmacist 2).

In terms of opportunity-related barriers, participants noted that they are limited in their ability to perform high-priority interventions by the nephrologists with whom they work. For example, one participant stated, "I work with about 13 different nephrologists and they all seem to do their own thing. So these are excellent guidelines and it was great to learn how rigorously they were came up with ... but having said that, as a pharmacist, we make a recommendation and then the nephrologist sometimes decides to do their own thing anyway" (Pharmacist 5).

Enablers of Implementation of Renal QI-DTP Interventions

Three themes were identified that reflected enablers of renal pharmacists' implementation of renal QI-DTP interventions (Table 5). One of the themes applied from the perspectives of both capability and motivation. According to this theme, participants who had received additional formal training, such as a pharmacy practice residency, felt more confident in performing high-priority interventions reflected in the QI-DTPs. For example, one participant stated, "I stepped away and went to school for a couple years just so that I could develop these skills. I'm pretty comfortable implementing these QIs and again lucky that I have the support of the nephrology team so I can actually make changes" (Pharmacist 9).

Table 5. Enabler Themes*

Category	Theme
Capability	Renal pharmacists who have received additional training (residency, PharmD) feel more confident in performing high-priority interventions.
Opportunity	Renal pharmacists can perform high-priority interventions when they have support from colleagues and nephrologists.
Motivation	1. Renal pharmacists want their patients to achieve the best health outcomes possible. 2. Renal pharmacists who have received additional training (residency, Pharm D) feel more confident in performing high-priority interventions.

*Based on the Behaviour Change Wheel, a tool that describes the behaviour of interest in terms of sources of capability, opportunity, and motivation (COM-B). According to the COM-B system, an individual must possess capability, motivation, and opportunity in order for behaviour change to occur.[12]

A second motivation enabler theme was also identified, whereby renal pharmacists wanted their patients to achieve the best health outcomes possible. For example, one participant stated, "I think it's our role to actually identify areas where you would implement the QI ... to communicate to the other health care providers working with us what we would want to implement and why" (Pharmacist 1).

Finally, there was one enabler theme related to opportunity. Participants stated that they could perform high-priority interventions when they had support from colleagues and nephrologists. For example, one participant stated, "I suppose a lot of it has to do with your communication with your nephrology team. Over the years you get comfortable with the people working on your team ... the nurses, nephrologist, etc. I think part of being able to do all of these interventions is having a trust and a comfort level with the team that you work with" (Pharmacist 3).

DISCUSSION

Previous studies have explored interventions that renal pharmacists can perform to improve patient outcomes.[17,18] For example, a 2012 study looked at pharmacists' interventions in the management of patients with chronic kidney disease, but the authors did not specifically examine which interventions had the most value for renal pharmacists to perform.[18]

Since there is no established standard of practice for renal clinical pharmacists in Canada, the set of 17 previously determined renal QI-DTP interventions may help pharmacists prioritize the patients they care for and the DTPs on which they intervene to improve the quality of care.[9]

This study was unique in using a framework that incorporates behaviour change theories such as the Theoretical Domains Framework and the Behaviour Change Wheel to elucidate specific barriers and enablers to performing renal QI-DTP interventions, as perceived by Canadian pharmacists, rather than considering a broader suite of clinical pharmacy performance indicators, such as medication reconciliation, patient education, and protocol development. Drug-related interventions such as the QI-DTP interventions cannot be effectively implemented without first determining what renal pharmacists see as barriers and enablers to performing them and then removing, modifying, or enhancing these barriers and enablers, as appropriate.

Six themes related to barriers and enablers to implementation of renal QI-DTP interventions were identified in this study, encompassing all 3 behaviour source components of the COM-B system. It is not surprising that capability was identified as both a barrier and an enabler, because a core component of capability is knowledge (or lack thereof). The well-trained renal pharmacists who participated in this study identified that improved knowledge is necessary for successful renal implementation of QI-DTP interventions. However, it was surprising that renal pharmacists did not consider the renal QI-DTP interventions to have the highest priority, despite the fact that they were developed by a panel of expert renal pharmacists using the highest-quality evidence. Perhaps this finding in itself reflects the other capability barrier, that renal pharmacists do not feel they have sufficient knowledge to perform priority interventions. Alternatively, perhaps it reflects participants' decreased motivation to perform interventions for which they do not believe they have the appropriate capability.

The opportunity-related barrier was related to limitations in pharmacists' perceived ability to perform high-priority interventions in collaboration with nephrologists. Stated differently, renal pharmacists felt that the QI-DTP interventions would not be supported by their nephrologist colleagues, who would be required to change an existing prescription to resolve the QI-DTP. These pharmacists generally viewed their role as medication advisors, with the nephrologist making the final decision to initiate or modify drug therapy for their patients. This opportunity-related barrier may also reflect a systematically different practice environment from the practice environment of the expert renal pharmacists who developed the renal QI-DTP interventions (e.g., small non-academic hospitals versus large academically affiliated institutions). Large academic institutions may have more support for continuing education and a more specialized practice, whereas community hospitals may require the renal pharmacist to cross-cover other areas, which would decrease time available to spend specifically on renal interventions. Moreover, this barrier may be related to the capability-related barrier of insufficient pharmacist knowledge or to the motivation-related barrier of perceived inability to perform these interventions. Conversely, the pharmacists who worked closely with other health care professionals on a multidisciplinary nephrology team stated that it would be relatively easy to implement these QI-DTP interventions, because they had the trust and support of the nephrologist and the nephrology team. It would be interesting to better understand nephrologists' views about this perceived opportunity barrier.

The enablers of implementation of renal QI-DTP interventions encompassed capability, opportunity, and motivation behaviour sources. From a capability standpoint, there is potential to engage renal pharmacists with background education and training beyond that of an entry-to-practice degree to enhance the implementation of QI-DTP interventions. Opportunity can be enhanced through engagement of renal pharmacists and nephrologists to build support for implementation of renal QI-DTP interventions. In terms of motivation, it is important to note that the pharmacists who had post–entry-to-practice training (residency or PharmD) appeared to demonstrate more confidence in their ability to implement the QI-DTP interventions than the pharmacists without this level of training. The pharmacists without post–entry-to-practice training acknowledged the importance of having a set of QI-DTP interventions in renal practice and stated that if they were to receive brief education or training on the QI-DTP interventions, they would most likely be able to incorporate them into their practice. This finding suggests that additional training may be beneficial in motivating pharmacists to perform renal QI-DTP interventions. Finally, implementation of renal QI-DTP interventions may be enhanced by harnessing renal pharmacists' motivation to achieve the best possible health outcomes for their patients.

This is one of only a few studies that have attempted to identify sources of desired behaviour related to renal pharmacy professional practice, and our methods led to several strengths. The sample of renal pharmacists was heterogeneous in terms of education and training background, and we had representation from most provinces across Canada. The interview questions were developed using a validated tool for identifying factors that influence behaviour change. The investigator who performed the interviews and coding kept a reflexive journal to improve the rigour and trustworthiness of the results, through transparency about the investigator's coding process.

The limitations of this study require discussion. The study relied upon volunteer participation, which might have introduced selection bias; as a result, the themes that we identified may not be applicable to the entire community of renal pharmacists. The participants who were interviewed may represent a more motivated subgroup of renal pharmacists than the general population of renal clinical pharmacists in Canada. We did not group participants according to whether they worked at an academic-affiliated institutions or a non–academic-affiliated institution, which might have affected pharmacists' success in performing interventions. A single investigator transcribed all of the interviews and performed most of the coding, which might have affected the rigour of our findings, as other investigators might have coded responses slightly differently and might have identified different themes from the same data. Finally, despite identifying only 12 of the 14 TDF domains, it is nonetheless possible that we reached code saturation, because participants might not have perceived the 2 unidentified domains (emotion, reinforcement) as either barriers or enablers. However, it is unlikely that interviewing additional renal pharmacists would have led to these 2 TDF domains being identified as barriers or enablers, because redundant information was provided by the existing sample of participants.

Future research should focus on soliciting patient feedback on the QI-DTP interventions to determine whether patients' medication priorities align with this consensus list and to obtain feedback on how patients learn about drug therapy and what type of information patients need to make decisions about medications. The information from these future studies will be used, in part, along with the barriers and enablers identified in this study, to help inform the development of an intervention to increase the uptake of QI-DTP interventions by renal pharmacists. Other research should aim to investigate some of the social influences identified as barriers in this study, such as perceived lack of support from nephrologists; those studies should involve the specific professionals assumed to be resistant to implementation of renal QI-DTP interventions. An understanding of these views could supplement the themes identified in the current study to strengthen the design of behaviour change interventions.

Finally, but most importantly, the priority for future research will be to incorporate the results of this study into the Behaviour Change Wheel to develop, implement, and evaluate proven behaviour change interventions aimed at overcoming the identified barriers and enhancing the enablers to implementation of renal QI-DTP interventions by renal pharmacists. By understanding the factors that influence renal pharmacists' clinical behaviour, interventions can be adjusted to more effectively modify behaviour. This future research will also provide an opportunity to evaluate the feasibility and success of these interventions. The ultimate goal is to improve renal patient outcomes by optimizing the pharmaceutical care that renal pharmacists deliver.

CONCLUSION

Renal clinical pharmacists identified 3 barriers and 3 enablers to implementation of renal QI-DTP interventions. Removing or modifying the barriers and optimizing the enablers might encourage renal pharmacists to perform these high-value interventions and improve the quality of care for renal patients.

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ORIGINAL RESEARCH

Pharmacist- or Nurse Practitioner–Led Assessment and Titration of Sacubitril/Valsartan in a Heart Failure Clinic: A Cohort Study

Arden R Barry and Candy Lee

ABSTRACT

Background: Sacubitril/valsartan is a first-in-class angiotensin receptor–neprilysin inhibitor indicated in the management of heart failure with reduced ejection fraction, based on the results of the PARADIGM-HF trial. Practice-based studies are needed to validate its effect in real-world settings. Clinical pharmacists are ideally situated to assess and titrate sacubitril/valsartan.

Objective: To evaluate the utilization, safety, and tolerability of sacubitril/valsartan in a multidisciplinary heart failure clinic, with assessment and titration by a clinical pharmacist or a nurse practitioner.

Methods: A retrospective cohort study was conducted at a heart failure clinic in Abbotsford, Canada. Included were adult patients with heart failure who were currently or formerly taking sacubitril/valsartan. Data collected for the period October 2015 to February 2019 included patient characteristics, New York Heart Association (NYHA) classification, concurrent medications, sacubitril/valsartan dose, adverse effects, and discontinuation rate.

Results: In total, 128 patients were included. Mean age was 70.1 years, 98 (77%) of the patients were men, and 79 (62%) had NYHA class 2 heart failure. The clinical pharmacist managed care for 78 (61%) of the patients, and the nurse practitioner managed care for 50 (39%). Forty-one (32%) of the patients met modified PARADIGM-HF inclusion criteria. Eighty-five (66%) of the patients achieved the target dose of sacubitril/valsartan, with similar proportions for the clinical pharmacist and nurse practitioner groups, over a mean of 2.2 clinic visits. Patients who achieved the sacubitril/valsartan target dose, relative to those who did not, were significantly younger and had higher mean systolic blood pressure at baseline. Twenty-nine percent of patients (35/119) had an improvement in NYHA classification from before initiation of sacubitril/valsartan to achievement of target or maximally tolerated dose. Eighty-five (66%) of the patients experienced an adverse effect, primarily hypotension, and 12 (9%) required a dose reduction. Only 9 (7%) patients discontinued therapy.

Conclusions: This study demonstrates the real-world safety and tolerability of sacubitril/valsartan in the treatment of heart failure, and reinforces

RÉSUMÉ

Contexte : Le sacubitril-valsartan est un inhibiteur novateur des récepteurs de l'angiotensine-néprilysine, indiqué dans la gestion de l'insuffisance cardiaque accompagnée d'une baisse de la fraction d'éjection, selon les résultats de l'essai PARADIGM-HF. Des études fondées sur la pratique sont nécessaires pour valider ses effets en contexte réel. Les pharmaciens cliniciens sont bien placés pour évaluer et titrer le sacubitril-valsartan.

Objectif : Évaluer l'utilisation, l'innocuité et le seuil de tolérance du sacubitril-valsartan en clinique multidisciplinaire d'insuffisance cardiaque, l'évaluation et le titrage étant effectués par un pharmacien clinicien ou une infirmière praticienne.

Méthodes : Une étude de cohorte rétrospective a été menée au sein d'une clinique d'insuffisance cardiaque à Abbotsford, au Canada. Les patients adultes inclus dans l'étude souffraient d'insuffisance cardiaque, ils prenaient ou avaient pris du sacubitril-valsartan. Les données recueillies entre octobre 2015 et février 2019 comprenaient les caractéristiques des patients, la classification de la New York Heart Association (NYHA), les médicaments pris de façon concomitante, la dose de sacubitril-valsartan, les effets secondaires et le taux d'abandon.

Résultats : Au total, 128 patients ont participé à l'étude. L'âge moyen des patients était de 70,1 ans, 98 d'entre eux (77 %) étaient des hommes et 79 (62 %) souffraient d'une insuffisance cardiaque de classe 2 selon la classification de la NYHA. Le pharmacien clinicien gérait les soins de 78 patients (61 %) et la pharmacienne praticienne gérait ceux de 50 patients (39 %). Quarante-et-un patients (32 %) répondaient aux critères d'inclusion modifiés de PARADIGM-HF. Quatre-vingt-cinq (66 %) patients atteignaient le dosage ciblé de sacubitril-valsartan dans des proportions similaires entre le groupe du pharmacien clinicien et celui de l'infirmière praticienne, à raison d'une moyenne de 2,2 visites en clinique. Les patients ayant atteint le dosage ciblé de sacubitril-valsartan, par rapport à ceux ne l'ayant pas atteint, étaient considérablement plus jeunes et leur tension artérielle systolique moyenne de base était plus élevée. Une amélioration de la classification NYHA a été observée chez 29 % des patients (35/119) entre le début de la prise de sacubitril-valsartan et l'atteinte du dosage ciblé ou de la dose maximale tolérée. Des effets

that clinical pharmacists can effectively assess and titrate medications in a multidisciplinary heart failure clinic.

Keywords: sacubitril/valsartan, angiotensin receptor–neprilysin inhibitor, heart failure, clinical pharmacists, clinical medicine

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secondaires ont été observés chez 85 patients (66 %), principalement une hypotension, et 12 d'entre eux (9 %) ont dû réduire la dose. Seuls 9 patients (7 %) ont dû abandonner la thérapie.

Conclusions : Cette étude démontre l'innocuité et le seuil de tolérance en contexte réel du sacubitril-valsartan pour le traitement de l'insuffisance cardiaque. Elle renforce le fait que les pharmaciens cliniciens peuvent efficacement évaluer et titrer des médicaments au sein d'une clinique d'insuffisance cardiaque multidisciplinaire.

Mots-clés : sacubitril-valsartan, inhibiteur des récepteurs de l'angiotensine-néprilysine, insuffisance cardiaque, pharmaciens cliniciens, médecine clinique

INTRODUCTION

Heart failure–associated mortality has improved over the past 30 years, which is attributable in part to several pharmacologic therapies, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), ß-blockers, and mineralocorticoid receptor antagonists.[1-6] However, substantial morbidity and mortality remain, with an estimated 5-year mortality rate of approximately 50%.[7] In the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubitril/valsartan, a first-in-class angiotensin receptor–neprilysin inhibitor, reduced cardiovascular deaths and heart failure hospitalizations relative to enalapril in patients with heart failure with reduced ejection fraction.[8] On the basis of this trial, contemporary North American heart failure guidelines now recommend sacubitril/valsartan in place of ACEIs/ARBs for patients who remain symptomatic despite appropriate guideline-directed medical therapy.[9,10]

The PARADIGM-HF trial had relatively strict inclusion criteria, specifically patients with heart failure with reduced ejection fraction, left ventricular ejection fraction (LVEF) less than or equal to 40%, New York Heart Association (NYHA) class 2–4 symptoms, and elevated serum B-type natriuretic peptide (BNP).[8] Furthermore, the PARADIGM-HF trial had an extensive run-in period, whereby only patients who tolerated target doses of both sacubitril/valsartan and enalapril underwent randomization. Thus, the results of the PARADIGM-HF trial may overestimate the tolerability of sacubitril/valsartan and patients' ability to achieve the target dose in a real-world setting. These factors highlight the need for observational studies to evaluate the use of sacubitril/valsartan in practice.

Studies have shown that medication management at multidisciplinary heart failure clinics reduces the risk of all-cause and heart failure hospitalizations, as well as all-cause mortality.[11,12] In addition, pharmacists have been shown to play an integral role in the care of patients with heart failure, including assessment and titration of guideline-directed medical therapy.[13] The purpose of the current study was to evaluate the utilization, tolerability, and safety of sacubitril/valsartan at a heart failure clinic with a multidisciplinary approach (clinical pharmacist or nurse practitioner) to assessment and titration.

METHODS

This retrospective cohort study was conducted at a tertiary heart failure clinic located at the Abbotsford Regional Hospital and Cancer Centre in Abbotsford, British Columbia. The study included all adult patients (≥ 18 years of age) with a clinical diagnosis of heart failure of any type who were currently or formerly taking sacubitril/valsartan. Patients with missing baseline data and those who died during sacubitril/valsartan titration were excluded.

Sacubitril/valsartan was approved by Health Canada in October 2015 and became eligible for publicly funded drug coverage in British Columbia in May 2018. Data for this study were collected retrospectively for the period from October 2015 to February 2019, with data collection occurring between July 2017 and February 2019. It was not possible to identify patients who were taking sacubitril/valsartan and who were discharged from the clinic before July 2017, because their paper-based outpatient medical records were unavailable. The 2 authors (C.L. from July 2017 to March 2018; A.R.B. from January 2019 to February 2019) collected the data from both paper-based and electronic medical records using a standardized data collection form. The study protocol was submitted to the Fraser Health Research Ethics Board, which deemed it to be a quality improvement project and thus exempt from review.

The heart failure clinic provides specialized cardiac care to an active roster of approximately 400 patients with heart failure in the Abbotsford region. It is staffed by a rotating group of 5 cardiologists and 1 internist, as well as 1 nurse practitioner, 2 registered nurses, 1 dietician, and 1 clinical pharmacist (A.R.B.). The clinical pharmacist provides consultative services, based on referrals, to assess and titrate all heart failure medications. For each patient, sacubitril/valsartan therapy was initiated by either a physician (cardiologist or internist) or the nurse practitioner. All

patients whose sacubitril/valsartan was initiated by a cardiologist or internist were referred to the clinical pharmacist (if available) for assessment and titration. These patients were typically scheduled to see the clinical pharmacist every 4–8 weeks (depending on availability) until they achieved the target or maximally tolerated dose of sacubitril/valsartan. For patients whose sacubitril/valsartan was initiated by the nurse practitioner, as well as those with initiation by a physician but for whom timely review (e.g., > 8 weeks) by the pharmacist could not be scheduled, the nurse practitioner performed assessment and titration. For each clinic visit, the clinical pharmacist or nurse practitioner performed a comprehensive patient assessment, including functional status (i.e., NYHA classification), medication review, laboratory monitoring, and physical assessment. Because the clinical pharmacist did not have prescribing privileges, all medication changes were briefly discussed with a cardiologist, internist, or the nurse practitioner to generate a verbal order. Once the target or maximally tolerated dose of sacubitril/valsartan was achieved, patients whose therapy was managed by the clinical pharmacist were referred back to the cardiologist or internist for further management of heart failure. The maximally tolerated dose was defined at the clinician's discretion, but was typically based on the patient experiencing an intolerable adverse effect at a higher dose or being considered to be at high risk of an adverse effect if the dose was increased. Patients who were not deemed to be receiving the maximally tolerated dose but were not at the target dose at the time of data collection were classified as being in the titration phase. Patients' tolerance of the target dose was assessed at a final follow-up clinic visit after the dose was increased.

For eligible patients, the following baseline data were collected: age, sex, cause of heart failure, NYHA classification, LVEF, comorbid medical conditions, blood pressure, serum potassium, serum creatinine, estimated glomerular filtration rate, serum BNP (within the preceding 12 months), concurrent heart failure medications (ACEI/ARB, ß-blocker, mineralocorticoid receptor antagonist), and starting dose of sacubitril/valsartan. The LVEF was recorded as the most recent assessment via echocardiography (as a mean if a range was provided), multigated acquisition radionuclide angiography, or magnetic resonance imaging. The following data were collected for each clinic visit: sacubitril/valsartan dose, NYHA classification, presence of adverse effects, sacubitril/valsartan discontinuation (if applicable), and reason for discontinuation (if applicable). The dose of sacubitril/valsartan was reported as the combined total of sacubitril and valsartan (i.e., 49/51 mg was reported as 100 mg). Symptomatic adverse effects were assessed by questioning patients about common adverse effects (e.g., light-headedness) or by self-reporting, and the patient's blood pressure and bloodwork (e.g., serum creatinine, serum potassium) were reviewed at each clinic visit at the clinician's discretion. Predefined adverse effects included mild hyperkalemia (defined as serum potassium 5.1–5.5 mmol/L), moderate hyperkalemia (defined as serum potassium > 5.5 mmol/L), hypotension (defined as systolic blood pressure < 100 mm Hg, diastolic blood pressure < 60 mm Hg, or symptoms of light-headedness associated with a reduction in blood pressure), and acute renal impairment (defined as ≥ 30% increase in serum creatinine from baseline). Any other potential adverse effects reported by the patient were also collected. Each adverse effect was counted only once for each patient. After the final clinic visit, the number of clinic visits (excluding the initial visit when sacubitril/valsartan was initiated), the sacubitril/valsartan dose, and the NYHA classification were collected.

The primary outcome was the proportion of patients for whom sacubitril/valsartan was prescribed who met modified PARADIGM-HF trial inclusion criteria (defined as NYHA class 2–4 symptoms, LVEF ≤ 40%, serum BNP ≥ 150 pg/mL, and ACEI/ARB and ß-blocker before initiation). Secondary outcomes were the proportion of patients who achieved the sacubitril/valsartan target dose (200 mg twice daily), number of clinic visits, rate and type of adverse effects, rate and reason for sacubitril/valsartan discontinuation, and change in NYHA classification from before sacubitril/valsartan initiation to achievement of target or maximally tolerated dose. As well, the following variables were compared between patients whose care was managed by the clinical pharmacist and those with care managed by the nurse practitioner: patient characteristics, proportion of patients who achieved the target dose of sacubitril/valsartan, number of clinic visits, rate and type of adverse effects, and rate of sacubitril/valsartan discontinuation.

The analysis was based on descriptive statistics. Categorical variables are expressed as frequencies with percentages. Continuous variables are expressed as means with standard deviations or medians with interquartile ranges (IQRs). Comparisons were made with an unpaired, 2-sided Student *t* test for continuous variables and a χ^2 test for categorical variables. All statistical analyses were performed with IBM SPSS Statistics (version 21, IBM Corporation, Armonk, New York). A 2-sided *p* value of less than 0.05 was considered statistically significant.

RESULTS

After review of approximately 700 medical records, 140 patients were identified as currently or formerly taking sacubitril/valsartan. Baseline data were unavailable for 9 of these patients, and 3 patients died during sacubitril/valsartan titration. Therefore, 128 patients were included in the analysis. Patient characteristics are summarized in Table 1. The mean total daily starting dose of sacubitril/valsartan was 149 (standard deviation [SD] 55) mg; of the 128 patients, 67 (52%) were started on 50 mg twice daily, 60 (47%) on 100 mg twice daily, and 1 (1%) on 200 mg twice daily. Forty-one patients (32%) met the modified PARADIGM-HF inclusion criteria (Table 2). The most common reason for not meeting the PARADIGM-HF criteria was lack of baseline serum BNP assessment.

Table 1. Baseline Patient Characteristics

Characteristic	Study Group; No. (%) of Patients*		
	Entire Cohort (*n* = 128)	Care by Clinical Pharmacist (*n* = 78)	Care by Nurse Practitioner (*n* = 50)
Age (years) (mean ± SD)	70.1 ± 11.6	70.0 ± 11.5	70.2 ± 11.8
Sex, male	98 (77)	59 (76)	39 (78)
LVEF (%) (mean ± SD)	29.4 ± 7.1	29.6 ± 7.0	29.2 ± 7.2
Serum BNP† (pg/mL) (median and IQR)	401 (168–1024)	296 (149–1060)	554 (185–1053)
Cause of heart failure			
Ischemic	63 (49)	39 (50)	24 (48)
Non-ischemic	57 (45)	35 (45)	22 (44)
Mixed	8 (6)	4 (5)	4 (8)
NYHA classification			
1	8 (6)	5 (6)	3 (6)
2	79 (62)	48 (62)	31 (62)
3	40 (31)	24 (31)	16 (32)
4	1 (1)	1 (1)	0 (0)
Comorbidities			
Hypertension	95 (74)	58 (74)	37 (74)
Coronary artery disease	73 (57)	44 (56)	29 (58)
Atrial fibrillation	50 (39)	30 (38)	20 (40)
Type 2 diabetes mellitus	47 (37)	25 (32)	22 (44)
Cerebrovascular disease	10 (8)	4 (5)	6 (12)
Medications			
ACEI or ARB	115 (90)	72 (92)	43 (86)
ß-Blocker	128 (100)	78 (100)	50 (100)
Mineralocorticoid receptor antagonist	88 (69)	56 (72)	32 (64)
Clinical measures (mean ± SD)			
Systolic blood pressure (mm Hg)	121.4 ± 18.9	122.8 ± 19.9	119.1 ± 17.2
Diastolic blood pressure (mm Hg)	72.3 ± 10.2	73.0 ± 10.3	71.2 ± 10.2
Serum creatinine (µmol/L)	113.2 ± 28.0	113.1 ± 28.8	113.3 ± 27.2
Estimated glomerular filtration rate (mL/min)	57.5 ± 18.2	57.5 ± 18.2	57.6 ± 18.2
Serum potassium (mmol/L)	4.5 ± 0.4	4.5 ± 0.4	4.5 ± 0.4

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = B-type natriuretic peptide, IQR = interquartile range, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, SD = standard deviation.
*Except where indicated otherwise.
†Data were available for only 65 patients.

Table 2. Comparison with Modified Inclusion Criteria* for the PARADIGM-HF Trial[8]

Variable	No. (%) of Patients† (*n* = 128)
Data available, met criteria	41 (32)
No baseline serum BNP	63 (49)
Baseline serum BNP < 150 pg/mL	15 (12)
Not taking ACEI or ARB at baseline	13 (10)
LVEF > 40%	8 (6)
NYHA class 1 at baseline	8 (6)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = B-type natriuretic peptide, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association.
*Modified inclusion criteria for the PARADIGM-HF trial were defined as NYHA class 2–4 symptoms, LVEF ≤ 40%, serum BNP ≥ 150 pg/mL, and receiving ACEI/ARB and ß-blocker before initiation.
†Percentages do not sum to 100 because some patients had more than one criterion not met.

Table 3. Dosing of Sacubitril/Valsartan

Dose	No. (%) of Patients (*n* = 128)
Achieved target dose (200 mg twice daily)	85 (66)
Maximally tolerated dose less than target	31 (24)
100 mg in the morning and 200 mg in the evening	1 (1)
100 mg twice daily	12 (9)
50 mg in the morning and 100 mg in the evening	3 (2)
50 mg twice daily	15 (12)
Still in titration phase at end of data collection	3 (2)
100 mg in the morning and 200 mg in the evening	1 (1)
100 mg twice daily	2 (2)
Discontinued therapy	9 (7)

The sacubitril/valsartan regimens are summarized in Table 3. In total, 85 patients (66%) achieved the target dose of sacubitril/valsartan. The mean total daily dose of sacubitril/valsartan achieved was 331 (SD 114) mg. The mean number of follow-up clinic visits was 2.2 (SD 1.0). Paired data for NYHA classification were available for 119 patients (93%). The median

NYHA classification was 2 (IQR 2–3) before sacubitril/valsartan initiation and 2 (IQR 2–2) after achievement of the target or maximally tolerated dose. Eighty (67%) of these 119 patients had no change in their NYHA classification, 35 patients (29%) had an improvement in NYHA classification, and 4 patients (3%) had a decline in NYHA classification after achieving the target or maximally tolerated dose of sacubitril/valsartan.

Adverse effects are summarized in Table 4. The most common adverse effect was hypotension. Twelve patients (9%) required a dose reduction of sacubitril/valsartan because of an adverse effect: 10 patients with hypotension (1 of whom was admitted to hospital) and 2 patients with hyperkalemia. Nine patients (7%) discontinued sacubitril/valsartan: 3 because of gastrointestinal issues (diarrhea, bloating, and/or constipation), 3 because of hypotension, and 3 for unknown reasons (for 1 patient, sacubitril/valsartan was discontinued in hospital; the other 2 self-discontinued the therapy). No cases of angioedema were observed.

Patients who achieved the target dose of sacubitril/valsartan (n = 85), relative to those who did not (n = 34), were significantly younger (68.2 years versus 73.6 years, p = 0.03) and had a higher mean baseline systolic blood pressure (123.8 mm Hg versus 113.3 mm Hg, p = 0.004). Furthermore, patients who achieved the target dose, relative to those who did not, had a lower rate of overall adverse effects (54% [46/85] versus 94% [32/34], p < 0.001), hypotension (26% [22/85] versus 85% [29/34], p < 0.001), and acute kidney injury (8% [7/85] versus 24% [8/34], p = 0.02). There was no significant difference between groups in the rate of mild hyperkalemia (36% [31/85] versus 35% [12/34], p = 0.90) or moderate hyperkalemia (4% [3/85] versus 12% [4/34], p = 0.09).

Sacubitril/valsartan assessment and titration was managed by the clinical pharmacist for 78 patients (61%) and by the nurse practitioner for 50 patients (39%). There were no statistically significant differences in baseline characteristics between the groups (Table 1). The mean number of clinic visits per patient was 2.1 (SD 1.0) for those in the clinical pharmacist group and 2.3 (SD 1.1) for those in the nurse practitioner group (p = 0.37). Of the 9 patients who discontinued sacubitril/valsartan, 4 had care managed by the clinical pharmacist and 5 had care managed by the nurse practitioner. Among the patients who continued sacubitril/valsartan therapy, 66% (49/74) of those with care managed by the clinical pharmacist achieved the target dose of sacubitril/valsartan, compared with 80% (36/45) of those with care managed by the nurse practitioner (p = 0.11). There were no significant differences in the rates of adverse effects between groups.

Table 4. Adverse Effects with Sacubitril/Valsartan

Adverse Effect	No. (%) of Patients (n = 128)
Any	85 (66)
Hypotension*	56 (44)
Mild hyperkalemia†	47 (37)
Acute kidney injury‡	16 (12)
Moderate hyperkalemia†	7 (5)
Diarrhea, bloating, constipation	3 (2)
Cough	1 (1)

*Defined as systolic blood pressure < 100 mm Hg, diastolic blood pressure < 60 mm Hg, or symptoms of light-headedness associated with a reduction in blood pressure.
†Mild hyperkalemia was defined as serum potassium 5.1–5.5 mmol/L; moderate hyperkalemia was defined as serum potassium > 5.5 mmol/L.
‡Defined as ≥ 30% increase in serum creatinine relative to baseline.

DISCUSSION

In this study, sacubitril/valsartan was generally well tolerated and safe for a select, real-world cohort of patients with heart failure. There were some differences between the present study population and patients in the PARADIGM-HF trial[8]—older age (70 versus 64 years), higher proportion of patients with NYHA class 3 heart failure (31% versus 23%), and higher median serum BNP (401 pg/mL versus 255 pg/mL)—which is consistent with other observational studies.[14-16] In other respects, patients were similar between the present study and the PARADIGM-HF trial: proportion of women (23% versus 21%), systolic blood pressure (121 mm Hg versus 122 mm Hg), serum creatinine (113 µmol/L versus 100 µmol/L), LVEF (29% versus 30%), and proportion with hypertension (74% versus 71%). Baseline use of ß-blockers and mineralocorticoid receptor antagonists was higher in the present study (100% versus 83% and 69% versus 54%, respectively). Only one-third of patients in the present study met the modified PARADIGM-HF criteria; however, this was primarily due to a lack of assessment of baseline serum BNP, which is not listed as a criterion for clinical use in the Canadian monograph for sacubitril/valsartan.[17] Therefore, it could be argued that use of sacubitril/valsartan in these patients was appropriate. Eight patients (6%) had LVEF over 40% and would not have been enrolled in the PARADIGM-HF trial. Notably, the recently published PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) demonstrated that among patients with LVEF of 45% or higher, sacubitril/valsartan improved NYHA classification but did not reduce the composite outcome of hospitalization for heart failure and death from cardiovascular causes.[18] Therefore, sacubitril/valsartan should be recommended only for patients with heart failure with reduced ejection fraction, which was the case for most of the patients in the present study.

Overall, approximately two-thirds of patients achieved the target dose, which is comparable to or higher than results in other observational studies.[14,15,19-21] One possible explanation is that the present study was conducted at a multidisciplinary heart failure clinic with titration of heart failure medication led primarily by a clinical pharmacist. As well, both the clinical pharmacist and the

nurse practitioner provided frequent follow-up (typically every 4–8 weeks) with a specific focus on sacubitril/valsartan assessment and titration. Inability to achieve the target dose of sacubitril/valsartan was likely secondary to the presence of adverse effects, as opposed to other factors such as status quo bias, inertia of previous practice, or lack of self-efficacy. Patients who experienced an adverse effect, particularly hypotension and acute kidney injury, were less likely to achieve the target dose. Accordingly, older patients and those with lower systolic blood pressure were at a higher risk of experiencing an adverse effect. A greater proportion of patients with care managed by the nurse practitioner, relative to those with care managed by the clinical pharmacist, achieved the sacubitril/valsartan target dose (80% versus 66%), although the difference was not statistically significant. This difference may have been due to variation in the baseline characteristics; specifically, more patients in the clinical pharmacist group were taking a mineralocorticoid receptor antagonist at baseline (72% versus 64%).

This study reinforces the concept that clinical pharmacists can effectively assess and titrate heart failure pharmacotherapy and supports the creation of pharmacist-led titration clinics to achieve guideline-directed medical therapy. The benefit of pharmacist involvement as part of a multidisciplinary team in the management of heart failure is well established. Studies have shown that medication management at multidisciplinary heart failure clinics reduces the risk of all-cause and heart failure hospitalizations, as well as all-cause mortality.[11,12] More specifically, pharmacist care of patients with heart failure has been shown to reduce both all-cause and heart failure–related hospitalizations.[13] In addition, pharmacist-led titration of heart failure medications in outpatient settings has been shown to increase the rate of achievement of target doses of ACEIs/ARBs and ß-blockers.[22-24] Pogge and Davis[19] showed that among 52 heart failure patients for whom sacubitril/valsartan was prescribed in a pharmacist-led clinic, 45 patients (87%) achieved the target dose.

In the present study, 29% of patients who were taking the target or maximally tolerated dose of sacubitril/valsartan had an improvement in their NYHA classification. However, the overall median NYHA classification did not change from baseline to achievement of the target or maximally tolerated dose. In other observational studies, sacubitril/valsartan has been associated with lower NYHA classification, as well as increases in LVEF and peak oxygen consumption and reductions in diuretic use, serum BNP, and hospitalizations.[14,20,25-28] Although 66% of patients in the present study experienced an adverse effect while taking sacubitril/valsartan, it did not typically lead to discontinuation, which is consistent with other literature.[15,20,28] Hypotension was markedly higher in the present study compared with the PARADIGM-HF trial (44% versus 14%), but was consistent with other observational studies.[15,20,28,29] Furthermore, the rate of hypotension was relatively high, despite a mean baseline blood pressure of roughly 121/72 mm Hg. Conversely, the rate of moderate hyperkalemia (serum potassium > 5.5 mmol/L) was approximately 5% in the present study, as opposed to 17% in the PARADIGM-HF trial. Although angioedema was not observed in the present study, this result was unsurprising, given that the incidence in the PARADIGM-HF trial was only 0.3%.[8]

This study had limitations that warrant discussion. It was a single-centre medical record review that relied on the completeness and accuracy of documentation. Because the study was primarily descriptive, no formal sample size calculation was performed for the comparison of patients with care managed by the clinical pharmacist versus the nurse practitioner. The observed improvement in NYHA classification for a small proportion of patients is compelling, because this result was based on a paired sample. However, other factors, such as fluid and sodium restriction and exercise, may have contributed to the observed improvement. Despite having objective criteria, the NYHA classification is a subjective assessment that is at risk of inter-user variability; however, this limitation may have been minimized by having the same clinician (clinical pharmacist or nurse practitioner) perform the assessment at each follow-up visit. Patients were followed only until they achieved the target or maximally tolerated dose of sacubitril/valsartan. Thus, further studies are warranted to evaluate the long-term safety and tolerability of sacubitril/valsartan in practice.

CONCLUSION

This study has demonstrated the real-world safety and tolerability of sacubitril/valsartan in the management of heart failure. More than two-thirds of patients achieved the target dose of the drug. Although the overall incidence of adverse effects (particularly hypotension) was common, these effects rarely necessitated discontinuation of therapy. This study reinforces that clinical pharmacists are effective in assessing and titrating heart failure medications in a multidisciplinary heart failure clinic.

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Point Prevalence Survey of Benzodiazepine and Sedative-Hypnotic Drug Use in Hospitalized Adult Patients

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ABSTRACT

Background: Benzodiazepines and sedative-hypnotic drugs (BZD/SHDs), such as zopiclone and the antidepressant trazodone, pose risks such as falls, fractures, and confusion, especially for older adults. Use of these drugs in the acute care setting is poorly understood.

Objectives: To determine the point prevalence and characteristics of use of BZD/SHDs in hospitals in Nova Scotia, Canada.

Methods: A point prevalence survey was conducted for adults admitted to all hospitals with at least 30 acute care beds between May and August 2016. Drugs administered intravenously, patients in long-term care, and patients receiving mental health services, addiction treatment, or critical care were excluded. The proportion of included patients who had received a BZD/SHD within the 24 h before the start of the survey was determined. A descriptive statistical analysis was performed.

Results: Overall BZD/SHD prevalence was 34.6% (487/1409) across the 16 eligible hospitals. The average age was 70.3 years, and 150 (30.8%) of the patients were 80 years or older. Among the 585 prescriptions for these patients, commonly used drugs were zopiclone (32.0%), lorazepam (21.9%), and trazodone (21.9%). The most common indications for use were bedtime/daytime sedation (60.0%) and anxiety (12.5%). More than half of the prescriptions (55.7%) had been initiated at home, 37.6% were started in hospital, and the place of initiation was unknown for 6.7%. Benzodiazepines were prescribed more frequently to patients under 65 years than those 80 years or older (41.3% versus 22.2%, $p < 0.001$) whereas trazodone was more frequently prescribed to the older of these 2 age groups (52.7% versus 14.3%, $p < 0.001$).

Conclusions: BZD/SHDs were frequently used by hospitalized adult patients in Nova Scotia. Trazodone appears to have been substituted for benzodiazepines in the oldest age group. Pharmacists should direct their efforts toward preventing inappropriate initiation of BZD/SHDs in hospital, particularly for elderly patients.

Keywords: benzodiazepines, sedative-hypnotic drugs, trazodone, hospital, geriatrics, sleep

RÉSUMÉ

Contexte : Les benzodiazépines et les médicaments sédatifs-hypnotiques (BZD/MSH), comme la zopiclone et l'antidépresseur trazodone, comportent des risques de chute, de fracture et de confusion, particulièrement chez les personnes âgées. Il existe une mauvaise compréhension de l'utilisation de ces médicaments dans un contexte de soins intensifs.

Objectifs : Déterminer la prévalence ponctuelle et les caractéristiques de l'utilisation des BZD/MSH dans des hôpitaux en Nouvelle-Écosse, au Canada.

Méthodes : Une enquête sur la prévalence ponctuelle a été menée entre mai et août 2016 auprès d'adultes admis dans les hôpitaux comptant au moins 30 lits en soins intensifs. Les patients recevant ces médicaments par voie intraveineuse, ceux en établissement de soins de longue durée, ceux recevant des services en santé mentale ou un traitement pour la toxicomanie ou encore ceux des soins intensifs ont été exclus de l'enquête. La détermination de la proportion des patients inclus dans l'étude portait sur ceux qui avaient reçu des BZD/MSH au cours des 24 h précédant le début de l'enquête, et elle a été suivie d'une analyse statistique descriptive.

Résultats : De manière générale, l'usage des BZD/MSH s'élevait à 34,6 % (487/1409) dans les 16 hôpitaux participants. L'âge moyen des patients était de 70,3 ans et 150 (30,8 %) étaient âgés d'au moins 80 ans. Parmi les 585 prescriptions pour ces patients, les médicaments communément utilisés étaient la zopiclone (32,0 %), le lorazepam (21,9 %) et le trazodone (21,9 %). Les indications d'utilisation les plus répandues concernaient la sédation au coucher et en cours de journée (60 %) et l'anxiété (12,5 %). Plus de la moitié des prescriptions (55,7 %) ont commencé à domicile, 37,6 % ont commencé à l'hôpital, et le lieu du début de la prise de ces médicaments était inconnu dans 6,7 % des cas. La prescription des benzodiazépines s'adressait plus souvent aux patients de moins de 65 ans qu'à ceux d'au moins 80 ans (41,3 % par rapport à 22,2 %, $p < 0,001$), tandis que la prescription de trazodone s'adressait plus souvent aux personnes de la tranche d'âge plus avancée (52,7 % par rapport à 14,3 %, $p < 0,001$).

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Conclusions : Les BZD/MSH étaient fréquemment utilisés par les patients adultes hospitalisés en Nouvelle-Écosse. La trazodone semble avoir remplacé les benzodiazépines dans le groupe plus âgé. Les pharmaciens devraient orienter leurs efforts sur la prévention de la prise inappropriée des BZD/MSH en hôpital, particulièrement par les patients plus âgés.

Mots-clés : benzodiazépines, médicaments sédatifs-hypnotiques, trazodone, hôpital, gériatrie, sommeil

INTRODUCTION

Sleep disturbances and anxiety are common in acutely ill, hospitalized adults.[1,2] The hospital environment and clinical care, such as blood tests and vital sign checks, can combine with the patients' illness, pain, reduced mobility, and medication adverse effects to disturb sleep.[3] Benzodiazepines (BZDs) and other sedative-hypnotic drugs (SHDs), specifically benzodiazepine receptor agonists (also called z-drugs), are commonly used to treat anxiety and insomnia. Trazodone, an antidepressant, is also frequently prescribed to adults for sleep.[4,5] However, use of these drug classes poses concerns in the acute care setting, including increased risk of falls, fractures, and hospital readmission, especially for older adults.[6-9] In some studies, hospitalized patients taking BZDs and z-drugs had higher odds of falling and experiencing severe injury.[7,10] At a rural hospital in Alberta, Canada, 55% of patients who had experienced a fall in hospital had a prescription for a BZD, and 38% had a prescription for an SHD such as zopiclone (a z-drug).[11] Trazodone has also been associated with daytime sedation, orthostatic hypotension, priapism, and falls leading to emergency department visits or hospital admissions, even at the low doses typically used for sleep disturbances.[5,12-14] As well, initiation of a BZD/SHD in the hospital setting can lead to continued use after discharge.[15-18]

Despite increased awareness of risks, deprescribing initiatives, and published guidelines that recommend avoiding the use of BZD/SHD in elderly patients,[19-21] there has been no marked decrease in prescribing rates in the community. In Canada, the United Kingdom, and Europe, slight decreases in benzodiazepine use have often been offset by increases in the use of z-drugs and, less frequently, trazodone.[14,22-26] In the United States, ambulatory visits associated with the prescribing of both benzodiazepines and z-drugs have increased among patients 65 years of age and older.[27] Utilization of BZD/SHDs in hospital settings is usually more frequent than in community settings, with rates as high as 62%.[15,28-31] It is not clear whether BZD rates are decreasing and/or BZDs are being substituted with other sedatives such as z-drugs and trazodone in hospitals. Published studies of sedative prescribing patterns have been limited to a single drug class (for example, benzodiazepines), to individual wards, or to academic hospitals in urban settings, which do not provide a broad view of current utilization.[15,16,28-30]

To better understand the use of sedatives in the hospital setting, we sought to determine the utilization of benzodiazepines, z-drugs, and trazodone (collectively termed BZD/SHDs) in adult hospitals in Nova Scotia, Canada. The information gained will assist our hospital, and potentially other health care organizations, to identify targets for quality improvement, as well as providing a baseline measure against which to evaluate the effectiveness of future interventions.[32,33] The primary objective of this study was to conduct a point prevalence survey of BZD/SHD utilization in the study hospitals. The secondary objectives were to determine the rate of initiation of BZD/SHDs in hospital and to characterize utilization in terms of specific drugs used, patients' age and sex, admitting service, hospital type, indication, dose, and whether the BZD/SHD was ordered with a preprinted order (PPO).

METHODS

Setting

A cross-sectional point prevalence survey was conducted in Nova Scotia, a Canadian province with a population of 953 900.[34] Canada has a universal public health care system in which medically essential services are provided by physicians and hospitals at no cost to patients.[35] The Nova Scotia Health Authority (NSHA) delivers health care services to Nova Scotians and specialized adult care to other nearby provinces.[36] The NSHA has one adult tertiary care centre, 9 regional hospitals, and more than 135 other community locations.[37] In 2016, there were almost 3200 hospital beds and more than 1 million inpatient days.[37] At the time of the survey, NSHA hospitals did not have a common drug formulary, electronic health record, or computerized physician order entry. Ethics approval to conduct the study was received on June 8, 2016, from the NSHA Research Ethics Board (file 1021365). Informed consent was not required because of the study design.

Hospital and Patient Selection

Hospitals with at least 30 acute care beds were included. Patients in transitional care (or alternate level of care) beds were included, because these patients are at risk due to frailty and older age. Transitional care patients are those who no longer require acute care services and are waiting for discharge to another setting, such as long-term care.[38] Hospitals were categorized by location,

according to the size of the population centre, as small and medium (< 100 000 residents) or large (≥ 100 000 residents).[39] Data were collected between June and August 2016. The survey of each individual ward was completed in 1 day, and surveys for all wards in a given hospital were completed within a 2-week period. Patient rosters were obtained from each hospital to identify the patients present on each audit day. Eligible patients were those 18 years of age or older who had been admitted for at least 24 h as of 0800 on the day of the survey. Patients were excluded if they had been admitted for psychiatric care, addiction treatment, or critical care, because these services would be associated with appropriate indications for sedatives (e.g., alcohol withdrawal, seizures, or conscious sedation). Long-term care residents and patients in the emergency department, whether visiting or waiting for admission to hospital, were also excluded.

Patients with documented administration of a benzodiazepine, a z-drug (zopiclone or zolpidem), or trazodone by the oral (including enteral or gastric tube), sublingual, subcutaneous, or intramuscular route, in the 24 h before 0800 on the day of the survey, were used to calculate the numerator. For the purposes of this study, medication use had to be documented on the patient-specific medication administration record. Other psychotropic drugs used off-label for sedation (e.g., antipsychotics) were not included because of the difficulty in determining the indication. Medications administered by the IV route were excluded because these would likely be associated with appropriate indications that were not of interest in this study (e.g., palliative care, critical care, alcohol withdrawal, treatment of seizures, or procedural use). The denominator was the total number of patients on the ward. Prevalence was calculated by dividing the numerator by the denominator for each population unit (e.g., ward, hospital, and province).

Training and Data Collection

A training manual was developed, and all co-investigators and 3 research assistants were trained in data collection procedures by the principal investigator (H.L.N.). The first 25 charts audited by each research assistant were assessed by the principal investigator for accuracy, and at least 10% of audited charts were assessed by a second member of the research team during the data collection period for quality control.

For patients with administration of a BZD/SHD according to the inclusion criteria, the following data were collected: age, sex, hospital admitting service, drug name, indication, dose, interval, route of administration, whether the medication was ordered on a PPO, total dose administered in the previous 24 h, and in-hospital initiation of the drug. A PPO is a hospital-approved set of orders designed to promote best practice and consistency in case management. For patients without administration of a BZD/SHD, no data were collected. The following ward information was collected: hospital name, ward name, specialty (e.g., medical), and number of beds. Orders for oxazepam, temazepam, trazodone, and z-drugs that were administered at bedtime were assumed to be given for sedation, because of the timing of the dose and the typical indications for these drugs. Data sources included the best possible medication history on admission, medication orders, records from the history and physical examination, progress notes, nursing notes, and medication administration records. All patients with administration of a BZD/SHD were given a unique study number; no personal identifiers were collected during the study.

Statistical Analysis

Data were entered into an Excel database (Microsoft Corporation, Redmond, Washington) by a research assistant and double-checked by a second research assistant. Results were

Table 1. Patient Characteristics and Point Prevalence of Benzodiazepines and Sedative-Hypnotic Drugs (BZD/SHDs) at Acute Care Hospitals in Nova Scotia (*n* = 1409)

Characteristic	Study Group; No. (%) of Patients		Prevalence, %
	Received a BZD/SHD	Did Not Receive a BZD/SHD	
All patients	487	922	34.6
Age (years)		Data not collected	Data not collected
< 65	152 (31.2)		
65–79	185 (38.0)		
> 79	150 (30.8)		
Sex, female	266 (54.6)	Data not collected	Data not collected
Population centre*			
Large	185 (38.0)	415 (45.0)	30.8
Small or medium	302 (62.0)	507 (55.0)	37.3
Specialty			
Medicine	303 (62.2)	541 (58.7)	35.9
Surgery	92 (18.9)	218 (23.6)	29.7
Transitional care	41 (8.4)	70 (7.6)	36.9
Other†	51 (10.5)	93 (10.1)	35.4

*Large population centres defined as ≥ 100 000 residents; small and medium population centres defined as < 100 000 residents.
†Rehabilitation, obstetrics, restorative care, mixed medicine/surgery.

summarized descriptively, and categorical data were analyzed by χ^2 tests with continuity correction for 2 × 2 tables to compare characteristics between groups of BZD/SHD users.

RESULTS

All 16 eligible hospitals participated in the point prevalence survey. Overall BZD/SHD point prevalence was 34.6% (487/1409). The point prevalence was 37.3% (302/809) for hospitals located in small and medium population centres, compared with 30.8% (185/600) for hospitals in large population centres (Table 1). Prevalence was higher among patients in transitional care (36.9% [41/111]) and medicine patients (35.9% [303/844]) than among surgical patients (29.7% [92/310]). Among the 487 patients who received a BZD/SHD, the mean age was 70.3 years (range 18–103 years), with most being over the age of 65 (*n* = 335 [68.8%]). The most common admitting service was medicine (*n* = 303 [62.2%]). Data collection by research assistants was audited by the research team for 97 (19.9%) of included patients, and any discrepancies were resolved at the time of the audit.

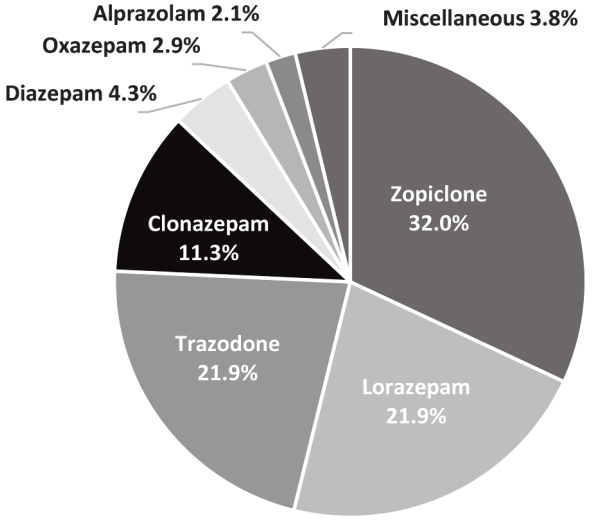

Figure 1. Specific benzodiazepine and sedative-hypnotic drugs prescribed in Nova Scotia hospitals, as proportions of all prescriptions for this group of drugs (*n* = 585).

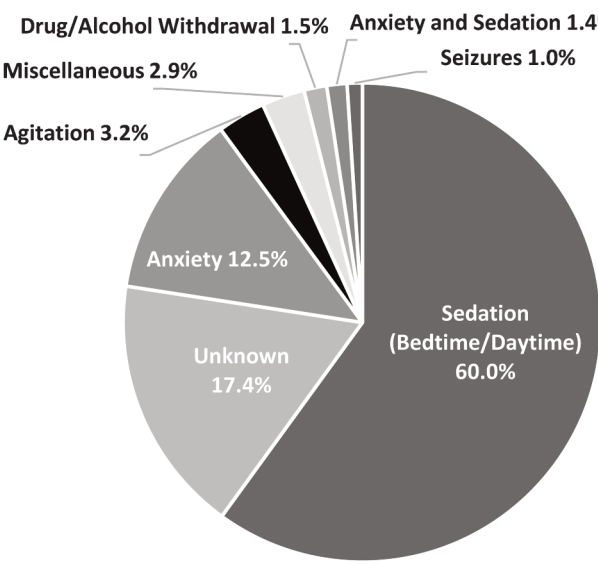

Figure 2. Indications for benzodiazepine and sedative-hypnotic drug prescriptions in Nova Scotia hospitals (*n* = 585 prescriptions).

There were a total of 585 BZD/SHD orders for the 487 patients, with 92 patients (18.9%) receiving more than 1 agent. The most commonly administered drugs are shown in Figure 1. Benzodiazepines as a class were the most frequently used BZD/SHD (*n* = 270 [46.2%]), but the top individual agents were zopiclone (*n* = 187 [32.0%]), trazodone (*n* = 128 [21.9%]) and lorazepam (*n* = 128 [21.9%]). Indications for use are depicted in Figure 2. Administration for sedation (*n* = 351 prescriptions) occurred at bedtime (*n* = 336 [95.7%]), both at bedtime and in the daytime (*n* = 13 [3.7%]), or in the daytime only (*n* = 2 [0.6%]).

Most BZD/SHDs were documented in written prescriptions (*n* = 549 [93.8%]), with relatively few documented in PPOs (*n* = 32 [5.5%]) or having unknown documentation (*n* = 4 [0.7%]). Four prescriptions could not be found in the paper charts because earlier chart information could not be located for long hospital admissions. The PPOs listed BZD/SHDs for the following indications: sedation (23), alcohol withdrawal (6), anxiety (2), and procedural use (1). Of the 10 PPOs that listed zopiclone, 3 did not adjust the dose according to the patient's age. PPOs were most often used on medicine units (23/32 [71.9%]).

Characteristics associated with whether the medications were initiated at home (*n* = 326 [55.7%]) or in the hospital (*n* = 220 [37.6%]) are presented in Table 2; for the remaining 39 orders (6.7%), the initiation setting could not be determined. Among BZD/SHD users, female sex and scheduled drug regimens were more frequently associated with the drugs being prescribed before admission ($p = 0.005$ and $p < 0.001$, respectively). "Take when needed" (PRN) prescriptions and PPOs were more frequently associated with the drugs being prescribed in hospital ($p < 0.001$ for both).

Patients' age distribution and BZD/SHD dosing information are provided in Table 3 and Table 4, respectively. Benzodiazepines were more frequently prescribed to patients less than 65 years old compared with patients 80 years of age or older (41.3% versus 22.2%, $p < 0.001$), whereas trazodone was more frequently prescribed to patients 80 years of age or older compared with patients less than 65 years old (52.7% versus 14.3%, $p < 0.001$). Prescription

Table 2. Prescriptions for Benzodiazepine and Sedative-Hypnotic Drugs in Relation to Setting Where Drug Was Initiated (*n* = 546)

Characteristic	Prescribing Setting; No. (%) of Patients*		*p* Value†
	Prescribed before Admission and Continued in Hospital	Prescribed in Hospital	
All prescriptions	326 (59.7)	220 (40.3)	
Specialty			0.28
Medicine (*n* = 335)	194 (57.9)	141 (42.1)	
Surgery (*n* = 111)	75 (67.6)	36 (32.4)	
Transitional care (*n* = 42)	25 (59.5)	17 (40.5)	
Other‡ (*n* = 58)	32 (55.2)	26 (44.8)	
Population centre§			0.42
Large (*n* = 222)	128 (57.7)	94 (42.3)	
Small or medium (*n* = 324)	198 (61.1)	126 (38.9)	
Sex			0.005
Female (*n* = 297)	194 (65.3)¶	103 (34.7)¶	
Male (*n* = 249)	132 (53.0)¶	117 (47.0)¶	
Drug regimen			< 0.001
Scheduled (*n* = 326)	239 (73.3)**	87 (26.7)**	
PRN (*n* = 206)	81 (39.3)**	125 (60.7)**	
Both scheduled and PRN (*n* = 14)	6 (42.9)	8 (57.1)	
Order type			< 0.001
Written order (*n* = 512)	324 (63.3)††	188 (36.7)††	
Preprinted order (*n* = 32)	2 (6.3)††	30 (93.8)††	
Unknown (*n* = 2)	0 (0)	2 (100)	

PRN = as needed.
*Percentages are calculated across rows, in relation to *n* value in column 1.
†Tested by χ^2.
‡Rehabilitation, obstetrics, restorative care, mixed medicine/surgery.
§Large population centres defined as ≥ 100 000 residents; small and medium population centres defined as < 100 000 residents.
¶Women were significantly different from men in terms of both drugs prescribed before admission and drugs prescribed while in hospital.
**Scheduled drug regimen was significantly different from PRN regimen for both drugs prescribed before admission and drugs prescribed while in hospital.
††Written orders were significantly different from preprinted orders for both drugs prescribed before admission and drugs prescribed while in hospital.

Table 3. Benzodiazepine and Sedative-Hypnotic Drugs Prescribed by Age Category in Nova Scotia Hospitals

Drugs Prescribed*	Age Group; No. (%) of Patients†				*p* Value‡
	< 65 years	65–79 years	≥ 80 years	All Patients	
All patients	152	185	150	487	<0.001
Benzodiazepine only	69 (41.3)§	61 (36.5)	37 (22.2)§	167	
Trazodone only	13 (14.3)¶	30 (33.0)	48 (52.7)¶	91	
Zopiclone only	37 (27.0)	52 (38.0)	48 (35.0)	137	
Any 2 sedatives	31 (36.0)**	38 (44.2)**	17 (19.8)**	86	
Any 3 sedatives	2 (33.3)	4 (66.7)	0	6	

*Patients were divided into 5 mutually exclusive groups: benzodiazepine (any), trazodone, zopiclone, any 2 sedatives (any combination, including multiple benzodiazepines), and any 3 sedatives (any combination, including multiple benzodiazepines).
†Percentages are calculated across rows, in relation to total number of patients in each mutually exclusive group based on drugs prescribed.
‡Tested by χ^2.
§Prescription of benzodiazepines was significantly different for age group < 65 years compared with age group ≥ 80 years.
¶Prescription of trazodone was significantly different for age group ≥ 80 years compared with age group < 65 years.
**Prescription of 2 sedatives was significantly different for age groups < 65 years and 65–79 years compared with age group ≥ 80 years.

of 2 sedatives at the same time was significantly associated with patients less than 65 years old and 65–79 years old compared with patients 80 years of age or older. As well, the mean dose decreased with increasing age, except for trazodone, for which the mean dose was 52.73 mg in patients 80 years of age or older and 51.68 mg in patients 65 to 79 years of age.

DISCUSSION

This point prevalence survey showed that BZD/SHDs were administered to approximately 35% of hospitalized patients in Nova Scotia over a 24-h period. This represents a substantial proportion of the general population in hospitals, given the

Table 4. Mean Dose* by Age Category for Benzodiazepine and Sedative-Hypnotic Drugs in Nova Scotia Hospitals

	Age < 65 years		Age 65–79 years		Age ≥ 80 years	
Drug†	***n***	**Mean Dose ± SD**	***n***	**Mean Dose ± SD**	***n***	**Mean Dose ± SD**
Clonazepam	23	1.07 ± 0.87	36	0.61 ± 0.43	7	0.50 ± 0.25
Lorazepam	62	1.12 ± 0.47	36	1.04 ± 0.48	30	0.89 ± 0.39
Trazodone	21	84.52 ± 51.52	52	51.68 ± 33.58	55	52.73 ± 28.33
Zopiclone	57	7.54 ± 2.97	72	6.65 ± 2.04	58	6.44 ± 2.52

SD = standard deviation.
*Mean total dose (mg) administered in the previous 24 h, or maximum prescribed dose if the dose was prescribed as a range and actual dose administered was not documented in the medication administration record (for which the following number of cases occurred: zopiclone, *n* = 5; trazodone, *n* = 7; lorazepam, *n* = 3).
†Data for other drugs were suppressed because of small sample sizes (≤ 5).

specific groups that were excluded from this analysis (e.g., critically ill patients, those receiving mental health services). The majority of use was for bedtime sedation of older patients on medicine units. Despite the well-known risks of BZD/SHDs, these results indicate that prevalence has not changed very much in the past 15 years, since the publication of 2 previous cross-sectional surveys in 2001 and 2005.[40,41] Those earlier surveys reported that benzodiazepines were prescribed for 21.2% to 36% of patients in the hospital setting, although actual administration to patients was not described.[40,41] In a more recent point prevalence survey involving an audit of various psychotropic medications, conducted in 2014, Brunero and others[28] reported that benzodiazepines were prescribed for 10% of patients. Those authors found that indications were not documented in 60% of prescriptions, a rate much higher than what was observed in our study. As well, 56% of the prescriptions in the earlier study were started in the hospital, compared with 37.6% in our point prevalence survey. Brunero and others[28] found that 44% of all psychotropics were continued upon discharge, whereas this type of information was not collected in our study.

Importantly, just over half of the BZD/SHDs prescribed to Nova Scotia inpatients were 2 non-benzodiazepine sedatives, zopiclone and trazodone, which supports community data that these drugs are replacing benzodiazepines.[14,22-25] Antipsychotics such as quetiapine, although not included in this study, are also replacing benzodiazepines because of their sedative properties.[14,16] Few reports have highlighted benzodiazepine substitution in hospitals. In a study conducted in 2013, Gillis and others[16] found that trazodone was the most commonly administered sedative in a hospital in Boston, Massachusetts (30% of patients), followed by lorazepam (24%) and z-drugs (18%). Although that study was a retrospective review of sedative use over a 2-month period, and not a point prevalence survey, the hospital's electronic medication administration system (rather than patient records) was used to document actual administered doses. Only a small number of patients were excluded from the study because the medication was ordered but not administered (15 out of 276 screened).[16] In contrast, Arnold and others[30] reviewed patient records over a 3-month period for psychotropic drugs administered to patients and found prevalences of 0.2% for trazodone and 12.6% for z-drugs. As well, when Schumacher and others[15] prospectively reviewed sedative drug use over a 3-month period using electronic medication administration data, they found low utilization of trazodone (1%) and z-drugs (11%).

It has been hypothesized that clinicians consider z-drugs and trazodone to be safer alternatives to benzodiazepines, particularly for elderly patients.[5,31] When we analyzed our data by age, we found that patients 80 years of age or older were more likely to have a prescription for trazodone and less likely to have a prescription for benzodiazepines alone or 2 different sedatives. Zopiclone use was fairly evenly distributed among all age groups. In the community setting, Alessi-Severini and others[22] found that z-drug use increased and BZD use decreased among residents over the age of 65 years over a 16-year period. Iaboni and others[14] compared changes in sedative use in community and long-term care settings from 2002 to 2013 in Ontario, Canada. They found that BZD use decreased while low-dose trazodone use increased among older adults. Overall, psychotropic drug use decreased among community-dwelling seniors, but those in long-term care received increasing numbers of prescriptions, due to significant increases in trazodone.[14] In our study, it was encouraging to note that a combination of 2 or more sedatives was prescribed less frequently to patients 80 years of age or older, in contrast to findings that psychotropic polypharmacy has increased among older adults in other settings.[14]

Elderly people are at greater risk of adverse effects from BZD/SHD use, particularly at higher doses.[42] Published guidelines, such as the Beers Criteria[20] and the Screening Tool of Older Person's Prescriptions (STOPP),[21] recommend against the use of BZDs and z-drugs because of the risk of delirium, cognitive impairment, falls, fractures, and motor vehicle accidents. Trazodone is not specifically mentioned in these guidelines; however, it would be covered by the Beers Criteria recommendation to minimize the use of central nervous system–active drugs to reduce the risk of falls.[20] The Choosing Wisely Canada toolkit for reducing BZD/SHD use by hospitalized older adults further reinforces the message that these medications are not the first choice for insomnia, agitation, or delirium.[43] In acute care hospitals in Nova Scotia, almost 70% of patients who received a BZD/SHD were over the age of 65, and 30% were over the age

of 80. Evaluation of average daily doses administered for the top 4 drugs in our study indicated that for most patients the dose did decrease with age; however, the mean zopiclone doses of 6.65 mg for patients 65 to 79 years of age and 6.44 mg for those 80 years or older (Table 4) were higher than recommended in the product monograph.[44] Canadian dosing guidelines suggest that for patients over 65 years of age, zopiclone should be started at 3.75 mg and titrated to 5 mg, to reduce the risk of impaired cognitive function and coordination, which have led to confusion and falls.[44]

Our point prevalence survey showed that BZD/SHDs were newly prescribed in hospital for 35% of patients, which is concerning because of the risk that sedatives initiated in hospital may be continued upon discharge.[16-18,45] Initiation of therapy in hospital is likely multifactorial, but could be triggered by use of a PPO. In our survey, only 32 orders originated from PPOs, but 94% of them were for newly prescribed BZD/SHDs. PPOs were more likely to be used in medicine wards. Freter and others[46] reported a PPO intervention to reduce delirium among orthopedic patients in one of the hospitals included in the current study. In the earlier study, intervention PPOs focused on scheduled analgesics and laxatives, trazodone (instead of benzodiazepines) for nighttime sedation, and other protocols. Benzodiazepine use was negligible, which the authors attributed to benzodiazepines not being listed on the PPOs and to previous educational efforts at the hospital. However, zopiclone (also not listed on the PPOs) was prescribed for patients in both intervention and control groups.[46] A retrospective chart review of sedative use by patients in another Canadian hospital found that 20.4% of potentially inappropriate prescriptions were ordered from a PPO set on admission or postoperatively.[29] These results suggest a quality improvement opportunity to review the use of sedatives listed on PPOs.

For most of the patients in our study, sedatives had been prescribed before admission, and this therapy was continued while they were in hospital; this finding was even more likely for female patients. It can be challenging to address long-term home therapy in the acute care setting: the patients are sick, hospital stays are often short, and safe withdrawal of a BZD/SHD can require weeks to months of dose tapering. Despite these challenges, a hospital admission may present an opportunity to initiate discontinuation of long-term BZD/SHD use. In one recent Canadian pilot study involving 50 patients over the age of 65 years, 64% successfully discontinued sedative drugs by 30 days after discharge without an increase in sleep-related disturbances.[47] Hospitalized patients who were occasional (3–6 times a week) and regular (daily) users were given educational material with instructions for tapering and stopping long-term sedative use. The deprescribing intervention was more successful for patients who started the tapering process in hospital (29/36, 81%) than for those who started after discharge (3/14, 21%).[47] Hospital-based initiatives could be combined with a community-based public health approach to deprescribing BZD/SHDs, although currently there is uncertainty about how this can best be accomplished.[31] Research does support a stepwise approach, such as engaging the patient and health care providers, initiating trials of dose tapering, employing nonpharmacologic treatment such as cognitive behavioural therapy, and seeking specialist help when indicated.[19,31,43,48] Pharmacists can play a leading role in hospital-based interventions, particularly in terms of providing patient education, advising on safe tapering protocols, and communicating and following up with primary care providers.

Limitations to our point prevalence survey included reliance on documentation in the health record and potential inaccuracy of data collection. We sought to minimize errors by double-checking at least 10% of charts and requiring independent data entry. Demographic characteristics (e.g., age, sex) of patients who did not receive BZD/SHDs were not collected, which restricted our analysis to those patients who used a BZD/SHD and thus limited our interpretation of the findings. As well, some drugs that might have been administered for sedation (e.g., antipsychotics, antihistamines, melatonin) were not audited. Antipsychotics are frequently prescribed to hospital patients for sedation but also for other indications.[14,16] Data collection occurred during the summer months when bed occupancy may be lower; however, the sample was still expected to be representative. A point prevalence survey measures drug use at one point in time; therefore, we were not able to follow patients to discharge to determine whether BZD/SHDs were continued. Finally, we assumed that when oxazepam, z-drugs, temazepam, and trazodone were given at bedtime, they were given for sedation and not for other indications (e.g., anxiety or to manage behaviour).

The strengths of this study included the comprehensive sample and the large group of medications surveyed. All eligible hospitals in Nova Scotia participated, representing small, medium, and large population centres. The survey results are therefore generalizable to the entire province and likely to other jurisdictions. Selected populations were purposively excluded (e.g., patients receiving mental health services, addictions treatment, and critical care), because these represented settings where use of these drugs is often for other indications, such as seizures or alcohol withdrawal. This allowed us to focus on areas where BZD/SHD use for insomnia and anxiety has been more problematic (e.g., medical and surgical settings).

CONCLUSION

This point prevalence survey showed that BZD/SHDs were frequently used by hospitalized patients in Nova Scotia, Canada, most of whom were 65 years of age or older. Two non-benzodiazepine drugs, zopiclone and trazodone, were responsible for more than 50% of sedatives prescribed. Pharmacists and other health care providers should direct their efforts toward reducing

BZD/SHD use in the community, preventing inappropriate initiation of BZD/SHD in hospital, and, when these drugs are used, prescribing the lowest effective dose to minimize harm and improve quality of patient care. Future research should examine all drugs that might potentially be used for sleep, such as antipsychotics, antidepressants, antihistamines, and melatonin. To successfully implement interventions aimed at reducing BZD/SHD use in hospital, it will be important to better understand the perspectives of patients, prescribers, and other health care providers and to identify facilitators of and barriers to use.

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ORIGINAL RESEARCH

Prescribing Patterns and Patient Outcomes for Bone and Joint Infections Treated with Cefazolin and Probenecid: A Retrospective Observational Study

Marci E Dearing, Sarah V Burgess, Valerie Murphy, Samuel Campbell, Lynn Johnston, and Tasha D Ramsey

ABSTRACT

Background: Previous studies have described the use of cefazolin with probenecid to treat uncomplicated skin and soft-tissue infections. Some prescribers are extrapolating from this evidence to treat more invasive infections, which have a greater potential for poor outcomes, including treatment failure that could lead to increased morbidity and mortality. Information supporting cefazolin with probenecid as effective treatment in this context is needed.

Objectives: To describe prescribing patterns and outcomes for patients who received cefazolin with probenecid for the treatment of bone and joint infections.

Methods: This single-centre retrospective study involved adult outpatients for whom cefazolin and probenecid were prescribed for bone and joint infections between April 1, 2012, and March 31, 2017. Patient charts were reviewed, and data were collected for clinical and microbiological variables using a standardized data collection form.

Results: In a total of 80 cases, the patient received cefazolin and probenecid for treatment of a bone or joint infection, of which 69 cases met the inclusion criteria. In most cases (n = 67), the patients were treated with cefazolin 2 g IV plus probenecid 1 g PO, both given twice daily. Completion of prescribed treatment occurred in 56 patient cases (81%), resolution of signs and symptoms in 53 (77%), readmission to hospital in 11 (16%), recurrence of infection in 6 (9%), and treatment failure requiring a change in therapy in 7 (10%).

Conclusions: The effectiveness of cefazolin and probenecid for the treatment of bone and joint infections appears to be similar to that of standard treatment, as reported in the literature. Antibiotic effectiveness is difficult to determine conclusively in a retrospective analysis, so these results should be interpreted with caution, but they may stimulate further research.

Keywords: cefazolin, probenecid, bone infection, joint infection, outpatient parenteral antimicrobial therapy

RÉSUMÉ

Contexte : Des études précédentes ont décrit l'utilisation de la céfazoline et du probénécide pour traiter les infections cutanées et les infections de tissus mous. Quelques prescripteurs extrapolent ces éléments probants pour traiter des infections plus invasives, dont les résultats risquent d'être défavorables, comme un échec du traitement pouvant entraîner une morbidité et une mortalité accrues. De l'information supplémentaire étayant l'efficacité du traitement à l'aide de la céfazoline et du probénécide dans ce contexte est nécessaire.

Objectifs : Décrire les modes de prescription et les résultats obtenus par des patients ayant reçu de la céfazoline et du probénécide pour traiter des infections osseuses et articulaires.

Méthodes : Cette étude rétrospective unicentrique porte sur des patients ambulatoires adultes à qui on a prescrit de la céfazoline et du probénécide pour traiter des infections osseuses et articulaires entre le 1er avril 2012 et le 31 mars 2017. L'examen des dossiers médicaux des patients a permis la récolte de données sur les variables cliniques et microbiologiques à l'aide d'un formulaire de recueil de données standard.

Résultats : Les patients, soit 80 cas en tout, ont reçu de la céfazoline et du probénécide pour traiter une infection osseuse ou articulaire et 69 de ces cas répondaient aux critères d'inclusion. Dans la plupart des cas (n = 67), les patients étaient traités avec de la céfazoline IV dosée à 2 g et du probénécide dosé à 1 g PO, les deux produits étant administrés deux fois par jour. Le traitement a été appliqué au complet dans 56 cas (81 %), la résolution des signes et des symptômes a eu lieu dans 53 cas (77 %), la réadmission à l'hôpital s'est produite dans 11 cas (16 %), les infections ont récidivé dans 6 cas (9 %) et le traitement s'est soldé par un échec et a nécessité un changement de thérapie dans 7 cas (10 %).

Conclusions : L'efficacité de la céfazoline et du probénécide dans le traitement des infections osseuses et articulaires semble être similaire à celle des traitements standard, comme le rapporte la littérature scientifique. L'efficacité des antibiotiques est difficile à déterminer de façon concluante dans une analyse rétrospective, ces résultats doivent donc être interprétés avec prudence, mais ils pourraient stimuler des recherches supplémentaires.

Mots-clés : céfazoline, probénécide, infection osseuse, infection articulaire, thérapie antimicrobienne parentérale des patients ambulatoires

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INTRODUCTION

Management of bone and joint infections can be challenging, as there are many different approaches to treatment, and outcomes may be poor, with significant complications and prolonged courses of antibiotics.[1] In an era when antimicrobial resistance, health care spending, and hospital capacity are serious public health issues, treatment strategies that address these concerns are paramount.[2] A treatment approach to bone and joint infection that takes into consideration antimicrobial stewardship, health care resources, and patient outcomes is essential.

Treatment of infection with cefazolin and probenecid was first described in the 1970s.[3,4] Cefazolin, traditionally given every 8 h for infections requiring IV treatment, is a narrow-spectrum antibiotic that is preferred for treating many pathogens implicated in skin and soft-tissue infections, as well as bone and joint infections. Probenecid, an oral uricosuric agent with no antimicrobial activity, impairs the renal excretion of cefazolin, thus extending its half-life.[5] A challenge for outpatient parenteral antimicrobial therapy, when the availability of home IV infusion pumps is limited, is balancing selection of an antimicrobial that has convenient dosing (such as once-daily ceftriaxone or ertapenem) but a broader-than-necessary spectrum of activity with antimicrobial stewardship.[2] Coadministration of cefazolin with probenecid allows once- or twice-daily administration and improves the suitability of cefazolin for use as outpatient parenteral antimicrobial therapy.[2,5]

The evidence for the combination of cefazolin and probenecid is limited to the treatment of skin and soft-tissue infections and gonorrhea; this drug combination has not been evaluated for other infections.[3,4,6,7] Nonetheless, extrapolation of the available evidence and pharmacokinetic principles has prompted some clinicians to use cefazolin with probenecid for other types of infections with susceptible pathogens. This combination has been prescribed at our institution for outpatient treatment of osteomyelitis, diskitis, septic arthritis, and prosthetic joint infections. These infections, most commonly caused by *Staphylococcus aureus*, are associated with high rates of relapse and recurrence.[8,9] They represent a significant burden to the health care system and require prolonged treatment with antimicrobials.[10] Inadequate treatment can result in devastating complications, such as loss of limb function, amputation, bone loss, and death.[8-10]

Outcomes related to osteomyelitis are challenging to study, in part because of the diverse nature of the infection.[9] Some researchers recommend against using the term "cure" because of the inherently high recurrence rate and the possibility of chronic infection, which make it difficult to determine treatment effectiveness.[8] A 2013 Cochrane systematic review estimated the long-term recurrence rate for osteomyelitis at approximately 20%.[11] Treatment failure rates for vertebral osteomyelitis have ranged from 10% to 30% in clinical trials.[12] One study reported recovery from septic arthritis in 53% to 69% of treated patients, depending on the treatment modality.[13] For prosthetic joint infections, treatment success rates ranged from 31% to 82% for prosthetic retention and debridement to 90% for 2-stage exchange procedures.[14]

The purpose of this study was to describe prescribing patterns and outcomes for patients who received cefazolin with probenecid as outpatient therapy for the treatment of osteomyelitis (including the vertebral form), diskitis, septic arthritis, and prosthetic joint infections either following discharge from hospital or in the emergency department of the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia.

METHODS

Study Design

This single-centre, retrospective, observational study utilized a chart review to collect information about patients' demographic and clinical characteristics. The chart review was approved as a quality assurance project by the Nova Scotia Health Authority Research Ethics Board, and the requirement for patient informed consent was waived.

Patient Population and Screening

The population of interest consisted of patients who received cefazolin and probenecid as outpatient therapy for treatment of osteomyelitis, diskitis, septic arthritis, or prosthetic joint infection. Databases within the hospital's electronic discharge medication reconciliation and pharmacy software (BDM Pharmacy, BDM IT Solutions Inc, Saskatoon, Saskatchewan) were searched for patients for whom cefazolin and probenecid were prescribed from April 1, 2012, to March 31, 2017.

Inclusion and Exclusion Criteria

The study included patients who received cefazolin and probenecid as outpatient therapy. Adult patients with osteomyelitis, diskitis, septic arthritis, or a prosthetic joint infection for whom cefazolin and probenecid were prescribed either while they were inpatients (as a test dose in preparation for home administration after discharge from the study hospital) or while they were outpatients receiving therapy in the emergency department, were eligible for inclusion. Patients were excluded if they were less than 18 years of age, if their home address and/or permanent residence was outside of Nova Scotia (which precluded follow-up after discharge), if they were discharged from hospital with antimicrobial therapy other than cefazolin and probenecid (because of susceptibility information that became available after the initial test dose of cefazolin and probenecid), or if cefazolin and probenecid were used to facilitate short-term treatment outside of hospital (e.g., a weekend pass) without prescription of a full course of therapy.

Outcome Measures

The primary outcome measure was the percentage of patients who successfully completed the intended course of cefazolin and probenecid therapy. Success was defined as documented completion of the intended cefazolin and probenecid therapy, whether or not oral antibiotics were used after the IV course to complete the prescribed duration of therapy or for suppression of chronic infection.

Secondary outcome measures were the percentages of patients for whom cefazolin and probenecid therapy was initiated with the following characteristics:

- resolution of infection, defined as initial and sustained resolution of signs and symptoms, microbiological cure (if results were available), and no additional IV antimicrobial therapy for treatment of the bone and joint infection at 12 months from the end of the cefazolin and probenecid course[15]
- readmission for inpatient antimicrobial therapy related to the bone or joint infection up to 12 months after completion of initial therapy[15]
- change in antibiotic therapy due to presumed treatment failure or recurrence of infection during the defined treatment course or initiated within 1 month after completion of cefazolin and probenecid (separate from step-down to planned oral therapy)
- all-cause mortality during cefazolin and probenecid treatment and up to 12 months after completing the cefazolin and probenecid treatment[15]
- step-down to oral antibiotics to complete the planned duration of therapy or for suppression of chronic infection
- adverse effect(s) of cefazolin and/or probenecid causing discontinuation and/or change in therapy during the defined treatment course

Data Collection

After eligible patients were identified, relevant data were collected from the scanned charts in the Horizon Patient Folder and Clinical Portal databases using a standard data collection form (see Appendix 1, available at https://www.cjhp-online.ca/index.php/cjhp/issue/view/198/showToc). Information collected included demographic data, clinical characteristics, prescribing patterns for cefazolin and probenecid, and the outcomes of interest. Other antimicrobial therapy related to treatment of bone or joint infection and prescribed at the time of admission, while in hospital, or at the time of discharge was also recorded.

Statistical Analysis

Descriptive statistics were used to analyze and report the primary and secondary outcomes as a percentage or a mean with standard deviation (SD), as appropriate.

The association of specific outcome measures with baseline characteristics (age, sex, creatinine clearance, immunocompromise or immunocompetence, recurrent or chronic infection, specific type of bone or joint infection, location of prosthetic joint infection), additional antimicrobial therapy, empiric therapy (defined as either absence of microbiological culture or no

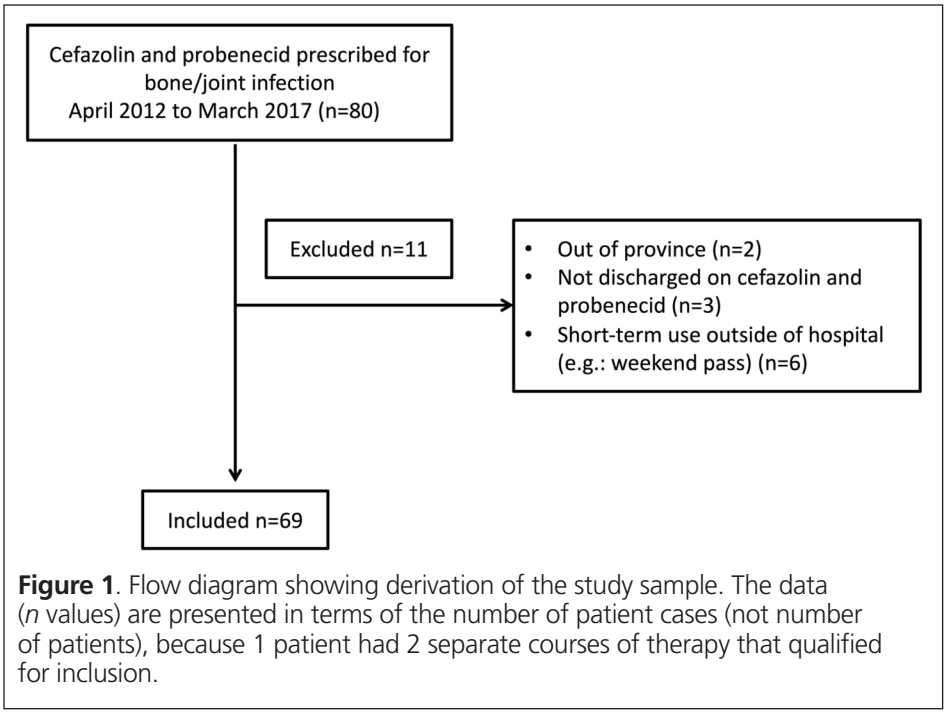

Figure 1. Flow diagram showing derivation of the study sample. The data (*n* values) are presented in terms of the number of patient cases (not number of patients), because 1 patient had 2 separate courses of therapy that qualified for inclusion.

growth), and monomicrobial or polymicrobial etiology was analyzed using univariate exact logistic regression. Results are reported as unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) and associated p values, with statistical significance defined as $p < 0.05$. The analysis was completed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

In a total of 80 patient cases, cefazolin and probenecid were prescribed for the treatment of a bone or joint infection. These cases represented a total of 79 patients, because 1 patient was treated on 2 separate occasions more than 12 months apart for infection in the same joint. Of the 80 patient cases, 69 met the inclusion criteria (Figure 1), including both treatment courses for the patient who had 2 treatments. Results are therefore presented in terms of patient cases (rather than patients) where appropriate. The baseline characteristics of the patient cases are presented in Table 1. Among the 69 patient cases, 33 (48%) were male, and the mean age was 62.0 (SD 14.1) years. In nearly half of the cases (n = 34 [49%]), there was prosthetic material in the infected area, 24 (35%) had a history of bone or joint infection, and 20 (29%) had a recurrent or chronic infection. The most common treatment indication was osteomyelitis (n = 29 [42%]), and the most common pathogen was methicillin-susceptible *S. aureus* (n = 31 [45%]). Fourteen (20%) of the patient cases were treated empirically. The mean duration of cefazolin and probenecid therapy was 36.0 (SD 16.1) days.

Almost all patient cases were treated with cefazolin 2 g IV twice daily preceded by probenecid 1 g PO twice daily (typically given 30 min before) (Table 2). One patient with a prosthetic joint infection received cefazolin 1 g IV preceded by probenecid 1 g PO, both given twice daily, and 1 patient with osteomyelitis received cefazolin 2 g IV preceded by probenecid 1 g PO, both given once a day. The reason for these lower doses was not clear from the patient records.

The prescribed course of cefazolin and probenecid therapy was completed in 56 patient cases (81%) (Table 3). Reasons for treatment not being completed as prescribed were intolerance, death, cefazolin resistance (as documented on susceptibility testing), patient's request for a once-daily regimen after starting treatment, recurrence of infection, and readmission to hospital (both related and unrelated to the infection) (Table 3). Prescribers determined the duration of cefazolin and probenecid treatment and the need for oral step-down therapy on the basis of clinical experience, patient factors, and infection characteristics (e.g., infection location or origin, pathogen, recurrence risk factors, presence of prosthetic material).

Step-down from IV to oral antibiotics occurred in 39 (57%) of the patient cases. Among these 39 cases, treatment with oral therapy was completed in 33 (85%) (for which mean duration of oral therapy was 61.5 days), and oral therapy was continued for suppression of chronic infection in 6 (15%). In most of these cases (27 [69%] of 39), IV therapy was stepped down to oral cephalexin.

Initial resolution of signs and symptoms was documented in 53 (77%) of all patient cases. In 49 (92%) of these 53 cases, resolution was sustained for a period of 12 months after the end of cefazolin and probenecid treatment. Of the 4 patient cases

Table 1. Baseline Characteristics

Characteristic	No. (%) of Cases* (n = 69)	
Sex		
Male	33	(48)
Female	36	(52)
Age (years) (mean ± SD)	62.0 ± 14.1	
Weight (kg) (mean ± SD)	88.6 ± 20.2	
BMI (mean ± SD)	31.3 ± 6.6	
Risk factors	66	(96)
Diabetes mellitus	27	(39)
Vascular insufficiency	11	(16)
Rheumatic disease†	30	(43)
Immunocompromise	9	(13)
Medication	4	(6)
Malignancy	5	(7)
Chronic kidney disease	4	(6)
Chronic liver disease	2	(3)
IV drug use	3	(4)
Obesity (BMI ≥ 30)	34	(49)
Peripheral neuropathy	9	(13)
Prosthetic material in infected area	34	(49)
History of bone or joint infection	24	(35)
Trauma	10	(14)
Intra-articular corticosteroid injection	2	(3)
Chronic limb ulcer	17	(25)
Diagnosis		
Prosthetic joint infection	18	(26)
Hip	6	(9)
Knee	11	(16)
Other	1	(1)
Osteomyelitis	29	(42)
Septic arthritis	5	(7)
Diskitis/vertebral osteomyelitis	17	(25)
Recurrent infection	20	(29)
Culture results		
Monomicrobial	37	(54)
Polymicrobial	18	(26)
No growth	9	(13)
Culture information unavailable	5	(7)
Microorganism(s) isolated		
MSSA	31	(45)
MSSA + other organism(s)	8	(12)
Coagulase-negative staphylococci	2	(3)
Streptococcus mitis	2	(3)
MRSA	0	(0)
Other	26	(38)

BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*, SD = standard deviation
*Except where indicated otherwise. The 69 patient cases represented a total of 68 patients; 1 patient had 2 separate courses of therapy that qualified for inclusion.
†Rheumatic disease includes rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and psoriatic arthritis.

Table 2. Cefazolin and Probenecid Prescribing Patterns and Related Treatment

Prescribing Patterns and Related Treatment	No. (%) of Cases* (*n* = 69)
Cefazolin and probenecid dose and frequency	
Cefazolin 2 g IV bid with probenecid 1 g PO bid	67 (97)
Cefazolin 1 g IV bid with probenecid 1 g PO bid	1 (1)
Cefazolin 2 g IV daily with probenecid 1 g PO daily	1 (1)
Duration of cefazolin and probenecid therapy (days) (mean ± SD)	
All diagnoses	36.0 ± 16.1
Prosthetic joint infection	42.9 ± 22.9
Osteomyelitis	33.7 ± 11.8
Septic arthritis	23.2 ± 13.3
Diskitis/vertebral osteomyelitis	36.4 ± 12.2
Duration of IV antibiotic therapy before cefazolin and probenecid (days) (mean ± SD)	11.0 ± 10.0
Antimicrobial therapy related to bone or joint infection, concurrent with cefazolin and probenecid	9 (13)
Rifampin	5 (7)
Metronidazole	3 (4)
Ciprofloxacin	1 (1)

SD = standard deviation.
*Except where indicated otherwise. The 69 patient cases represented a total of 68 patients; 1 patient had 2 separate courses of therapy that qualified for inclusion.

without sustained resolution up to 12 months, 2 involved prosthetic joint infections and 2 involved osteomyelitis. Initial resolution was not achieved in 16 (23%) of the patient cases, and sustained resolution was not achieved in 20 (29%) of all patient cases. Time from the start of any IV antimicrobial therapy to initial documented resolution was 89.2 (SD 46.4) days.

Readmission to hospital related to infection was documented in 11 (16%) of the patient cases. Seven cases required readmission during treatment, and 4 required readmission after completion of the prescribed course of cefazolin and probenecid. Recurrence of infection was documented in 6 (9%) of the patient cases. Treatment failure requiring a change in therapy at any time during the initial month after completion of the cefazolin and probenecid treatment occurred in 7 patient cases (10%).

Five of the patients in this study died. Three of these patients were receiving palliative care at the time of admission, all because of malignancy. For the fourth patient, palliation was started approximately 6 months after the end of treatment with cefazolin and probenecid, also because of malignancy. For the fifth patient, the goal of therapy was transitioned from cure to palliation of symptoms within 6 months of treatment completion with cefazolin and probenecid. This patient had multiple comorbidities, including severe peripheral vascular disease with several chronic ulcers, chronic heart failure, diabetes mellitus, and chronic obstructive pulmonary disease.

Table 3. Outcomes and Related Data

Outcome	No. (%) of Cases* (*n* = 69)
Completion of cefazolin and probenecid	
Yes	56 (81)
No	13 (19)
Adverse drug reaction	3 (4)
Death	1 (1)
Non-susceptible organism	1 (1)
Refusal of twice-daily treatment after start of therapy	1 (1)
Readmission, recurrence	7 (10)
Initial resolution of infectious signs and symptoms†	53 (77)
Prosthetic joint infection (*n* = 18)	16 (23)
Osteomyelitis (*n* = 29)	23 (33)
Septic arthritis (*n* = 5)	3 (4)
Diskitis/vertebral osteomyelitis (*n* = 17)	11 (16)
No resolution	
Readmission, recurrence, treatment failure	7 (10)
Adverse drug reaction	3 (4)
Palliative at admission	3 (4)
Refusal of twice-daily treatment	1 (1)
Noncompliance, IV drug use	1 (1)
Non-susceptible organism	1 (1)
Sustained resolution of infectious signs and symptoms at 12 months	
Yes	49 (71)
No	
Receiving palliative care within 12 months after treatment	2 (3)
Readmission, recurrence	2 (3)
Time to achieve documented resolution‡ (days) (mean ± SD)	89.2 ± 46.4
Readmitted to hospital for antimicrobial therapy related to initial infection	11 (16)
Treatment failure requiring change in therapy	7 (10)
Died	5 (7)
Receiving palliative care at time of admission	3 (4)
Step-down from IV to oral antibiotics	39 (57)
To complete duration of antibiotic therapy	33 (48)
Suppression of chronic infection	6 (9)
Step-down by specific drug	
Cephalexin	27 (39)
Cefuroxime	3 (4)
Penicillin	2 (3)
Amoxicillin-clavulanate	2 (3)
Cephalexin/rifampin	1 (1)
Ciprofloxacin/rifampin	1 (1)
Levofloxacin/rifampin	1 (1)
Ciprofloxacin/amoxicillin-clavulanate	1 (1)
Amoxicillin	1 (1)
Adverse effects causing change in therapy or discontinuation	
Any adverse effects	3 (4)
Nausea/vomiting	2 (3)
Clostridioides difficile	1 (1)

SD = standard deviation.
*Except where indicated otherwise. The 69 patient cases represented a total of 68 patients; 1 patient had 2 separate courses of therapy that qualified for inclusion
†The *n* values in column 1 indicate the number of patients with each type of infection.
‡From start of IV antimicrobial therapy related to bone/joint infection.

Adverse effects thought to be due to cefazolin and probenecid resulted in a change of therapy in 3 patient cases. Gastrointestinal adverse effects such as nausea and vomiting were responsible for 2 of these changes in therapy, whereas the third patient experienced *Clostridioides difficile* infection.

Several characteristics were associated with favourable or poor outcomes. Male sex (OR 5.52, 95% CI 1.30–33.71, $p = 0.016$) and immunocompetence (OR 5.39, 95% CI 0.99–32.05, $p = 0.052$) were associated with greater likelihood of documented resolution. Those with recurrent or chronic infection had higher odds of readmission (OR 5.86, 95% CI 1.26–31.85, $p = 0.021$). Recurrent or chronic infection (OR 15.25, 95% CI 1.54–771.86, $p = 0.013$) and any history of bone or joint infection (OR 11.16, 95% CI 1.14–559.68, $p = 0.034$) were associated with greater odds of recurrence or relapsed infection.

DISCUSSION

To our knowledge, the combination of cefazolin with probenecid administered as antimicrobial therapy for bone and joint infections has not previously been described. Despite this lack of evidence, its use to facilitate IV antibiotic therapy for such infections in the outpatient setting has become common practice at our institution. We believe that this retrospective observational study is the first to describe prescribing patterns and patient outcomes associated with cefazolin and probenecid for treatment of bone and joint infections.

In more than 80% of patient cases, the clinical response to the intended course of cefazolin and probenecid was sufficient to allow clinicians to consider the treatment appropriate for discontinuing further IV antimicrobial therapy. These results suggest that the combination of cefazolin and probenecid may be a reasonable component of antimicrobial therapy for bone and joint infections and hence that further exploration in controlled studies is warranted. Seventy-nine percent of patient cases involving osteomyelitis had initial resolution of infection, which is comparable to the approximately 70% treatment success rate reported in the literature.[16] In those with septic arthritis, the resolution rate was 60%, also comparable to the 53%–69% reported in the literature.[13] However, in our study, only 5 patients had septic arthritis, which makes it difficult to interpret and compare our findings for this specific population. The initial-resolution rate of 89% for cases of prosthetic joint infection is at the higher end of previously reported success rates (31%–90%).[14] Four patient cases had initial resolution that was not sustained over the long term. For 2 of these patient cases, both involving osteomyelitis, the goal of care was transitioned, within 12 months of treatment, from cure to palliation of symptoms (one possibly related to chronic infection, one unrelated). The remaining 2 patient cases involved prosthetic joint infections, and the patients were readmitted to hospital with recurrent infection. Documented resolution was not solely related to efficacy of treatment; other factors, such as adverse drug effects or death for reasons unrelated to the infection, may have led to absence of documented resolution (Table 3).

Almost all patient cases had 1 or more risk factors associated with a bone or joint infection ($n = 66$ [96%]), which have been linked to worse outcomes in the literature.[10] Those with a history of bone or joint infection had significantly higher odds of relapse or recurrence of infection, and those with recurrent or chronic infection had significantly higher odds of relapse or recurrence of infection or readmission to hospital. These results are to be expected, given that recurrence of infection occurs frequently in this population.[11]

The pathogen most often identified in this study was methicillin-susceptible *S. aureus*, comparable to what has been documented in the literature.[9,10] In our study, 20% of patient cases were treated empirically for the entirety of their treatment course, but the use of empiric therapy did not correlate with worse outcomes.

Concerns have been raised about the tolerability of probenecid, given that it has been associated with gastrointestinal upset, including nausea and vomiting. Only 4% of the patient cases in this study had a gastrointestinal adverse effect leading to discontinuation of therapy; in 1 patient, the cause of discontinuation was *C. difficile*, which is known to be correlated with antimicrobial therapy and not probenecid. However, there may have been selection bias in this study, given that a test dose of cefazolin and probenecid is prescribed before discharge for patients at our institution to demonstrate tolerability.

In our study, a regimen of cefazolin 2 g IV and probenecid 1 g PO, both twice daily, was prescribed for 97% of patient cases (Table 2). This regimen for cefazolin corresponds with the regimen of 2 g every 12 h suggested by the pharmacokinetic modelling of Spina and Dillon.[17] These authors assessed the ability of probenecid to achieve therapeutic cefazolin serum concentrations for the treatment of cellulitis, although their modelling analyzed probenecid 500 mg PO 4 times a day.[17] Doses reported in the literature for skin and soft-tissue infections are variable,[6,7,18] and our findings may be used to guide prescribing for bone and joint infections.

The limitations of this study include its retrospective and observational nature. Our analysis was limited to the data available in our databases and was reliant on the quality of documentation. Patient records were screened on the basis of available databases, which may not have captured all patients treated with this drug combination. Another limitation is the absence of an active comparator group receiving standard treatment; therefore, we compared our patient outcomes with those described in the literature.

Our results may not be generalizable to those who are more acutely ill, because the patients in this study were stable enough to be discharged home from hospital. Most of our patient cases

were seen by an infectious diseases physician, which could have led to selection bias, with more complex cases (e.g., cases with more comorbidities, cases with chronic infections) being included in the study; less complex cases might be treated differently and might have different outcomes. Access to an infectious diseases physician may not always be feasible, and these specialists may be more comfortable with this treatment strategy than other physicians. Finally, this study had a relatively small sample size, and the results should be interpreted with caution.

Future research should involve larger prospective evaluations of this combination of medications, with comparison to the standard of care, to assess efficacy and safety of use in patients with bone and joint infections. The effectiveness of cefazolin and probenecid for other invasive infections, such as bacteremia and endocarditis, should also be evaluated.

CONCLUSION

In most patient cases in this study, a regimen of cefazolin 2 g IV and probenecid 1 g PO, both twice daily, was prescribed. The use of cefazolin and probenecid for the treatment of bone and joint infections appears to have had comparable outcomes to what has been described in the literature for standard treatment, with completion of therapy for 81% of patient cases, and an overall rate of initial documented resolution of infection of 77%, sustained for 12 months in 71%. The results of this small, single-centre retrospective analysis should be interpreted with caution but may be used to guide future research.

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Vasopressin for Septic Shock in a Medical-Surgical Intensive Care Unit

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ABSTRACT

Background: Critically ill patients often need vasopressors to treat hypotension related to septic shock and to maintain adequate systemic perfusion. Although the 2017 guidelines of the Surviving Sepsis Campaign recommend norepinephrine as first-line therapy, they also state that vasopressin may be considered as an adjunctive agent for patients with refractory shock. Limited evidence is available for directing optimal administration of vasopressin. As such, prescribing practices are not standardized and may vary according to the particular clinician, the clinical scenario, and various patient-specific factors.

Objectives: To review the current practice of administering concomitant norepinephrine and vasopressin therapy to patients with septic shock, to describe variability in vasopressin administration, and to evaluate effects on patient safety in a medical-surgical intensive care unit (ICU).

Methods: This single-centre retrospective chart review involved 100 adult patients admitted to the ICU who received vasopressin and norepinephrine for septic shock between April and December 2017. The data were analyzed with descriptive statistics.

Results: The mean time to initiation of vasopressin was 12.0 (standard deviation [SD] 21.6) h after initiation of norepinephrine. The mean dose of norepinephrine at the time of vasopressin initiation was 29.5 (SD 19.7) µg/min. The mean vasopressin dose prescribed was 0.04 (SD 0.03) units/min, with a range of tapering and discontinuation regimens. The mean duration of vasopressin therapy was 49.1 (SD 65.2) h, and vasopressin was discontinued before norepinephrine in 49 of the patients. A total of 60 hypotensive events occurred after vasopressor discontinuation and were more common when vasopressin was discontinued before norepinephrine.

Conclusions: Vasopressin dosing was comparable to that reported elsewhere; however, discontinuation practices were inconsistent. These results show that variability in the literature supporting vasopressin use has led to variability in vasopressin administration and discontinuation practices; however, correlation with improvement in clinical outcomes, such as mortality or ICU length of stay, is unclear, and further research is required to determine the ideal approach to vasopressin use.

RÉSUMÉ

Contexte : Les patients gravement malades nécessitent souvent un vasopresseur pour traiter l'hypotension liée au choc septique et pour préserver une perfusion systémique adéquate. Bien que les directives de 2017 de la campagne Surviving Sepsis recommandent la norépinephrine en guise de thérapie de première ligne, elles précisent également que la vasopressine pourrait être envisagée comme agent d'appoint pour les patients présentant des chocs réfractaires. Seules des données probantes limitées soutiennent l'administration optimale de la vasopressine. Les pratiques de prescription proprement dites ne sont pas standardisées et peuvent varier selon le clinicien, le scénario clinique et les divers facteurs particuliers au patient.

Objectifs : Examiner la pratique actuelle d'administration de la norépinephrine concomitante à la thérapie de vasopressine aux patients ayant subi un choc septique, décrire la variabilité d'administration de la vasopressine et évaluer les effets sur la sécurité du patient dans une unité de soins intensifs (USI) médicale-chirurgicale.

Méthodes : Cet examen rétrospectif unicentrique des dossiers portait sur 100 patients adultes admis dans une USI, ayant reçu de la vasopressine et de la norépinephrine en réponse à des chocs septiques entre avril et décembre 2017. Les données ont été analysées à l'aide de statistiques descriptives.

Résultats : Le temps moyen du début de l'administration de la vasopressine était de 12 h (écart type [É.T.] 21,6) après le début de l'administration de la norépinephrine. La dose moyenne de norépinephrine au moment du début de l'administration de la vasopressine était de 29,5 (É.T. 19,7) µg/min. La dose moyenne de vasopressine prescrite était de 0,04 (É.T. 0,03) unités/min, avec une gamme de posologies dégressives et d'abandons. La durée moyenne de la thérapie à la vasopressine était de 49,1 h (É.T. 65,2), et 49 patients ont abandonné la vasopressine avant l'abandon de la norépinephrine. Un total de 60 événements hypotenseurs se sont produits après l'abandon du vasopresseur et ils étaient plus fréquents lors de l'abandon de la vasopressine précédant celui de la norépinephrine.

Conclusions : Le dosage de vasopressine était comparable à celui indiqué dans d'autres études; cependant, les pratiques d'abandon étaient

Keywords: norepinephrine, vasopressin, intensive care unit, septic shock

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incohérentes. Ces résultats démontrent que l'indétermination de l'information publiée dans la littérature soutenant l'utilisation de la vasopressine a entraîné une fluctuation dans l'administration de la vasopressine et des pratiques d'abandon; cependant, la corrélation entre l'usage de la vasopressine et l'amélioration des résultats cliniques, comme la mortalité ou la durée du séjour en USI, n'est pas claire, et davantage de recherches sont nécessaires pour déterminer l'approche idéale à adopter à l'égard de l'utilisation de la vasopressine.

Mots-clés : norépinephrine, vasopressine, unité de soins intensifs, choc septique

INTRODUCTION

Sepsis and septic shock are associated with circulatory failure in response to an infective and inflammatory process, leading to high in-hospital mortality rates, including in the intensive care unit (ICU). Sepsis is defined as life-threatening organ dysfunction caused by an unregulated host response to infection.[1] Patients with sepsis may experience distributive shock (of which septic shock is the most common form), a condition in which tissue perfusion decreases through a variety of vasodilatory mechanisms, metabolic and cellular abnormalities, and a prothrombotic state leading to microvascular thrombosis.[1,2] In the ICU, septic shock is the most common cause of death and is associated with complications such as irreversible organ dysfunction and prolongation of ICU and hospital length of stay.[2-5] The 2017 guidelines of the Surviving Sepsis Campaign (SSC) for management of septic shock provide evidence-based recommendations on immediate fluid resuscitation, administration of broad-spectrum antibiotics, and initial vasopressor therapy.[6]

Refractory hypotension is treated with vasopressors to increase systemic vascular resistance and therefore perfusion, which increases oxygen delivery to essential organ tissue, thereby minimizing cellular injury and death.[1] According to the SSC guidelines, norepinephrine is the first-line vasopressor used to maintain target mean arterial pressure in patients with septic shock (strong recommendation, moderate quality of evidence).[6] This drug exhibits its vasoconstrictive effects through agonism, primarily on α-adrenergic receptors, with lesser effects on ß-adrenergic receptors, thus leading to an increase in global systemic vascular resistance.[3] In recent years, small trials and a systematic review and meta-analysis have suggested that the adjunctive use of catecholamine-sparing agents such as vasopressin may improve survival in this clinical context.[4,7] Concomitant infusion of vasopressin may be used in cases of refractory septic shock to reach or maintain target mean arterial pressure and/or to decrease catecholamine requirements, which may prove particularly beneficial for patients with malignant arrhythmias or increased myocardial demand associated with high catecholamine load.[6,7] Conversely, each additional medication increases the potential for complications and adverse effects. As such, the addition of adjunctive agents is based on the clinician's judgment, taking into account various patient-specific factors.

Arginine vasopressin is a non-adrenergic vasoconstrictor that restores serum osmolality, blood volume, and pressure by directly constricting vascular smooth muscle.[3,5] Vasopressin increases intracellular calcium by direct action on G protein–coupled vascular (V1) receptors, causing vasoconstriction; it also inhibits the cytokine interleukin-1, decreasing vascular endothelial production of nitric oxide and thereby reducing nitric oxide–mediated vasodilation.[3,5] These vasoconstrictive effects are less pronounced in the cerebral, coronary, and renal vasculature, which makes vasopressin an appealing alternative for patients in whom these effects may be particularly deleterious.[3,5] Furthermore, it has been proposed that septic shock induces a vasopressin-deficient state[8-14]; a vasopressin infusion may thus replenish the depleted endogenous supply, in addition to providing essential hemodynamic support. Unlike norepinephrine, vasopressin has no effect on the ß-adrenergic receptor; hence, it may be an attractive therapeutic alternative for maintaining hemodynamic stability in patients exhibiting dysrhythmias, particularly those requiring high doses of catecholamines.[3,5,15]

There is limited evidence about the optimal dose and titration of vasopressin. Although there has been substantial heterogeneity in the dose of vasopressin administered in various studies (ranging from 0.01 to 0.1 units/min), low doses of this drug have consistently been associated with a reduction in norepinephrine requirements to maintain target blood pressure, with inconsistent effects on clinically relevant outcomes.[4,6-10,13] Higher doses have not shown additional clinical benefits in terms of survival or the number of kidney failure–free days.[8] One meta-analysis reported a small mortality benefit when patients received vasopressin as an adjunct to norepinephrine.[13] The VASST trial (Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock) compared the adjunctive use of vasopressin and norepinephrine with norepinephrine alone in patients with initiation of vasopressors for septic shock.[4] Although the patients did not exhibit vasopressor-refractory shock (mean arterial pressure 72 mm Hg at the time of randomization), the study found no difference in overall mortality, length of stay, or

adverse effects; however, a subgroup analysis suggested a reduction in 28-day mortality when vasopressin was used in patients who required lower doses of norepinephrine (5–14 μg/min).[4] Other researchers have hypothesized that early addition of vasopressin, in conjunction with steroids, may reduce the progression of organ failure and shorten the duration of shock, but their study results have been inconclusive.[4,8,16-18] Previous studies have shown that discontinuation of vasopressin before norepinephrine may lead to more episodes of "clinically significant hypotension", but does not correlate with a difference in clinically relevant secondary outcomes such as mortality or ICU length of stay.[10,14]

Optimal dosing, titration, indications, and duration of vasopressin therapy remain controversial. Despite conflicting and limited evidence regarding positive effects on outcomes, particularly in patients with refractory septic shock, our institution continues to routinely use vasopressin (0.04 units/min) as adjunctive therapy to norepinephrine, with variation among clinicians with regard to time of vasopressin initiation, duration of therapy, tapering discontinuation, and other aspects of therapy.

The purpose of this study was to review current practice at the study institution, to identify variability in the use and administration of vasopressin for septic shock in the medical-surgical ICU setting, and to evaluate the effects on patient safety, with a view to determining whether any intervention is required. The primary objective was to describe the use of vasopressin as an adjunctive vasopressor in adult patients with septic shock who were admitted to the medical-surgical ICU. The secondary objective was to describe the incidence of hypotensive events after discontinuation of vasopressin.

METHODS

This research study was approved by the local research and ethics board. The institutional review body waived the need for informed consent, given the quality improvement nature of the study.

Patients were identified on the basis of *International Classification of Diseases, 9th Revision* codes for septic shock. Patient records were reviewed sequentially in reverse chronological order, starting with December 2017, until a total of 100 patients meeting the inclusion criteria were identified. Adult patients who were admitted to the ICU and who were receiving vasopressin and norepinephrine for septic shock were included.

Septic shock was defined according to the 2017 SSC guidelines.[6] The SSC guidelines did not include the clinical criteria of the Third International Consensus Definitions for Sepsis and Septic Shock, known as Sepsis-3 (i.e., quick Sepsis-Related Organ Failure Assessment [qSOFA]),[1] because those criteria were not used in the studies that informed the recommendations in the 2017 revision of the SSC guidelines. In accordance with the SSC guidelines, septic shock was based on the presence of 2 or more of the following diagnostic criteria: systemic inflammatory response syndrome (temperature > 38 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min), proven or suspected infection, new dysfunction of a least one organ, hypotensive events despite adequate fluid resuscitation (where hypotension was defined as systolic blood pressure < 80 mm Hg, diastolic blood pressure < 50 mm Hg, and mean arterial pressure < 60 mm Hg), and/or IV norepinephrine requirement of at least 5 μg/min for 6 h.[6] Patients receiving vasopressin for brain death, hepatorenal syndrome, or acute cardiac resuscitation were excluded.

Data were collected and recorded by 2 investigators (A.P., A.B.), using a standardized data collection form. Ten percent of the charts from which data were collected were checked by co-investigators to ensure no inter-rater variability. The following information was collected: patient demographic characteristics, admission diagnosis, recent surgical history, Acute Physiology and Chronic Health Evaluation (APACHE) II score, pre-existing comorbidities, source of infection, pathogen type as confirmed by culture, hemodynamic variables at initiation of vasopressin therapy, initial fluid resuscitation volume received, dosage and duration of norepinephrine therapy, dosage and duration of vasopressin therapy, concomitant use of other vasopressors and/or inotropes, 28-day mortality, duration of mechanical ventilation, length of hospital admission, number of days in the ICU, onset of new organ failure during vasopressin therapy, use of renal replacement therapy, and concomitant use of corticosteroids. Occurrences of hypotension, defined as systolic blood pressure less than 80 mm Hg, diastolic blood pressure less than 50 mm Hg, mean arterial pressure less than 60 mm Hg, requirement for re-initiation of vasopressin, or requirement for increased dose of norepinephrine, were collected for up to 4 h after cessation of vasopressin.

Descriptive statistics were used to analyze the collected data. The findings are reported using quantitative analyses, such as mean with standard deviation or median with interquartile range for continuous variables and percentages for categorical variables.

RESULTS

A total of 100 patients admitted to the ICU between April and December 2017 were included in the analysis. The baseline characteristics of these patients, along with data concerning the numbers of patients requiring renal replacement therapy and/or mechanical ventilation, the ICU length of stay, and all-cause 28-day mortality, are presented in Table 1. The mean time to vasopressin initiation was 12.0 (SD 21.6) h after norepinephrine initiation (Table 2). The mean dose of norepinephrine at the time of vasopressin initiation was 29.5 (SD 19.7) μg/min. The mean vasopressin dose prescribed was 0.04 (SD 0.03) units/min, with a range of tapering and discontinuation regimens observed. The mean duration of vasopressin therapy was 49.1 (SD 65.2) h. Among the 49 patients in whom vasopressin was discontinued

Table 1. Demographic and Baseline Characteristics

Characteristic	No. of Patients* (*n* = 100)
Sex, male	65
Age (years) (median and IQR)	65 (52–75)
Weight (kg) (median and IQR)	84 (70–103)
APACHE II score (median and IQR)	27 (22–31)
Hemodynamic variables (mean ± SD)†	
Systolic blood pressure (mm Hg)	83.7 ± 16.4
Mean arterial pressure (mm Hg)	58.2 ± 11.2
Heart rate (beats/min)	98.2 ± 27.3
Lactate (mmol/L)	5.0 ± 4.6
White blood cells (× 10^9/L)	18.2 ± 13.3
Pre-existing conditions and medications	
Immunosuppression‡	47
Ischemic heart disease	32
Diabetes	33
Chronic renal failure	27
Antiarrhythmic drugs§	17
Chronic obstructive pulmonary disease	17
Alcohol misuse disorder	14
Congestive heart failure	10
Cirrhosis	9
Recent surgical history	31
Admission diagnosis	
Sepsis or infection¶	60
Post–cardiac arrest	9
Acute renal failure	8
Pancreatitis	6
Gastrointestinal bleeding	4
Other**	13
Source of infection	
Lung	43
Abdomen	3
Genitourinary	18
Skin and soft tissue	16
Blood	30
Unknown	3
Pathogen type in culture	
Gram-positive	63
Gram-negative	60
Fungal††	9
Mechanical ventilation (days) (median and IQR)	4.6 (2.2-7.9)
Renal replacement therapy during vasopressin	
Continuous renal replacement therapy	34
Intermittent hemodialysis	3
Hospital length of stay (days) (mean ± SD)	26.9 ± 26.9
ICU length of stay (days) (mean ± SD)	9.8 ± 9.9
All-cause 28-day mortality	55

APACHE II = Acute Physiology and Chronic Health Evaluation II, IQR = interquartile range, SD = standard deviation.
*Except where indicated otherwise.
†Recorded from time of initiation of the first vasopressor infusion.
‡Defined as receipt of immunosuppressive medications or absolute neutrophil count between 500 and 1000 × 10^9/L.
§Including sodium-channel blockers and potassium-channel blockers.
¶Any of the following types of sepsis or infection: pneumonia, urosepsis, postoperative sepsis, cellulitis, intra-abdominal infection, necrotizing fasciitis, endocarditis, febrile neutropenia, bacteremia, axillar abscess, sepsis of unknown etiology.
**Includes metabolic acidosis, metformin overdose, ruptured esophagus, congestive heart failure, hemoptysis, parastomal hernia, Stevens-Johnson syndrome.
††Fungal pathogens found by sputum or urine culture were excluded because of their nonpathogenic nature.

Table 2. Characteristics of Medication Therapy

Characteristic	Mean ± SD* (*n* = 100)
Norepinephrine	
Dose at vasopressin initiation (μg/min)	29.5 ± 19.7
Dose during vasopressin infusion (μg/min)	21.4 ± 17.2
Change in dose 4 h after vasopressin initiation (μg/min)	–2.8 ± 14.4
Change in dose 4 h after vasopressin discontinuation (μg/min)	+0.2 ± 3.1
Total duration (h)	78.9 ± 81.3
Vasopressin	
Time of initiation, relative to initiation of norepinephrine therapy (h)	+12.0 ± 21.6
Initial dose (units/min)	0.04 ± 0.03
Mean dose (units/min)	0.037 ± 0.005
Discontinuation dose (units/min)	0.01 ± 0.01
Total duration (h)	49.1 ± 65.2
Discontinued before norepinephrine† (no. of patients)	49
Corticosteroid‡	
Received corticosteroid therapy during vasopressin therapy (no. of patients)	35
Hydrocortisone dose equivalent (mg/day)	343.5 ± 289.7
Total duration (days)	2.3 ± 2.0
Other inotropes and vasopressors§ (no. of patients, *n* = 51)	
Epinephrine	28
Dobutamine	21
Phenylephrine	9
Milrinone	3

*Except where indicated otherwise.
†For a total of 33 patients, norepinephrine and vasopressin were discontinued at the same time. For 19 of these patients, discontinuation was due to withdrawal of care.
‡Includes any IV corticosteroid therapy, with all doses converted to hydrocortisone equivalents.
§Refers to use of these drugs at any point during the duration of vasopressin therapy.

before norepinephrine, the mean dose of norepinephrine at the time of vasopressin discontinuation was 7.8 (SD 6.8) μg/min.

There was an overall decrease (–2.8 [SD 14.4] μg/min) in mean norepinephrine dose once vasopressin was initiated. Approximately one-third of the patients (*n* = 36) experienced no change in norepinephrine requirement to maintain target mean arterial pressure once the vasopressin was discontinued, whereas 18 patients experienced an increase in norepinephrine requirement (+4.3 [SD 2.9] μg/min), and 13 experienced a decrease (–4.5 [SD 4.3] μg/min). A total of 14 patients had simultaneous discontinuation of norepinephrine and vasopressin, which suggests resolution of shock; another 19 patients had withdrawal of care. The mean total cost of vasopressin therapy per patient was $77.80 over a mean duration of 49.1 h. Additional data regarding the regimen of concurrent vasopressin and norepinephrine therapy are presented in Table 2.

In this study, a total of 60 hypotensive events occurred after discontinuation of vasopressor therapy. Forty-one of these hypotensive episodes occurred among the 49 patients with discontinuation of vasopressin before norepinephrine, whereas

9 episodes occurred among the 18 patients with discontinuation of norepinephrine before vasopressin. The remaining 10 hypotensive events occurred in the group of 14 patients with discontinuation of both agents at the same time. For 19 patients, no hypotensive events were captured because vasopressors were discontinued as a result of withdrawal of care. Other than these hypotensive events, the only major adverse effect observed was digital ischemia, experienced by 3 patients.

Approximately one-third of the patients (n = 35) received systemic corticosteroid therapy during vasopressin infusion, and half (n = 51) received other vasopressors and/or inotropes in addition to vasopressin and norepinephrine, which suggests severe refractory or multifactorial shock. A total of 24 (69%) of the 35 patients who received some form of IV corticosteroid died before the 28-day mortality marker. Details about corticosteroid and additional vasopressor/inotrope therapy are presented in Table 2.

Thirty-seven patients required renal replacement therapy while receiving vasopressin (Table 1), none of whom had previously been receiving long-term renal replacement therapy before admission. Data concerning new-onset organ dysfunction during vasopressin therapy appear in Table 3.

Table 3. Clinically Significant Organ Dysfunction While on Vasopressor Therapy

New Organ Dysfunction	No. of Patients (n = 100)
Renal dysfunction*	42
Hepatic dysfunction†	69
Respiratory failure‡	94

*Defined as any of the following: serum creatinine (SCr) 3 times patient's baseline level, increase in SCr to ≥ 4 mg/dL (≥ 353.6 µmol/L), initiation of renal replacement therapy, urine output < 0.3 mL/kg/h for ≥ 24 h, or anuria for ≥ 12 h.
†Defined as any of the following: international normalized ratio ≥ 1.5 (not receiving anticoagulation), increased alanine aminotransferase or aspartate aminostransferase (> 3 times upper limit of normal), bilirubin greater than 3 times upper limit of normal, thrombocytopenia (platelet count < 150 × 10^9/L).
‡Defined as mechanical ventilation and ratio of partial pressure of arterial oxygen to fraction of inspired oxygen < 300 mm Hg.

DISCUSSION

At the study institution, practices for the concomitant use of norepinephrine and vasopressin for septic shock aligned with current guidelines, and vasopressor therapy was initiated after appropriate fluid resuscitation for refractory shock.[6] Because the VASST trial showed no difference in 28-day mortality between concurrent vasopressin and norepinephrine therapy and norepinephrine alone,[4] it has been suggested that doses of vasopressin greater than 0.03 units/min may be required in severe septic shock. A small case-control study suggested significant improvement in mean arterial pressure when vasopressin was administered at 0.04 units/min; however, supporting evidence on clinical outcomes such as mortality remains unclear.[9] Of note, the mean dose documented in the current study was lower than the dose of 0.06 units/min studied in the VANISH trial (Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients with Septic Shock), which showed no improvement in renal failure–free days but increased rates of ischemic events.[8] In most cases in the current study, vasopressin was initiated at a dose of 0.04 units/min, and the dose remained stable for the duration of therapy; however, once discontinuation was ordered by the physician, the vasopressin tapering regimens implemented by nursing staff were variable.

As expected, vasopressin initiation facilitated an overall decrease in the hourly rate of norepinephrine infusion to maintain target mean arterial pressure. Although a subgroup analysis in the VASST trial suggested a mortality benefit of vasopressin in patients deemed to have less severe shock,[4] this description applied to only a minority of our patient population. Although mean APACHE II scores in the current study were comparable to those in the VASST trial, approximately 75% of patients (n = 73) required norepinephrine doses of 15 µg/min or more before vasopressin initiation, and nearly one-third of all patients (n = 31) were receiving more than 35 µg/min, which suggests that our sample included patients who presented with more refractory shock and thus greater risk of death than those in previous trials.

Pneumonia was the most common cause of sepsis, and one-third of patients had microbiologically confirmed bacteremia, which is consistent with the prevalence reported previously[2]; however, the all-cause 28-day mortality rate (55%) was higher than expected, which supports the suggestion of higher severity of illness.[4,8] Given the nature of this study, no conclusions can be drawn about the effect of vasopressin on mortality. Our findings suggest that vasopressin is used as a catecholamine-sparing agent in patients requiring high levels of norepinephrine support to maintain hemodynamics in the treatment of septic shock.

Vasopressin was more commonly discontinued before norepinephrine in this study, which previous research has suggested may increase the likelihood of clinically significant hypotension,[10] because of the body's inability to regain endogenous function of vasopressin after cessation of exogenous vasopressin. Although hypotension after vasopressor cessation occurred more frequently in patients whose vasopressin was discontinued before norepinephrine, it was largely transient in nature and often required no additional vasopressor support. Half of the patients exhibited no change in norepinephrine requirements 4 h after vasopressin was stopped, which suggests clinical improvement and possible resolution of the shock state. Given the elimination half-life of vasopressin, any changes in vasopressor requirements beyond this time frame would likely be attributed to a change in the patient's clinical status rather than to discontinuation of vasopressin. In light of the retrospective nature of the study and variable nursing practices for tapering vasopressin, we are unable to draw conclusions about the optimal approach to vasopressin discontinuation in relation to clinical outcomes.

Dobutamine and epinephrine were most common among the other vasopressors and inotropes used for the patients in this study. Of the patients who received epinephrine, fewer than half survived to the 28-day mortality marker, which suggests that this vasopressor may be added for patients with more severe refractory shock. The prevalence of use of dobutamine and epinephrine suggests that a number of patients exhibited elements of cardiogenic shock. Similar to the use of epinephrine, administration of IV corticosteroids was also associated with higher mortality.

Identification of adverse events was limited to those documented in the interdisciplinary progress notes. Because of the retrospective nature of the study, adverse reactions could not be reliably attributed to specific drug therapy, and causality due to medications could not be established. The SSC guidelines note that vasopressin infusion at a rate higher than 0.03 units/min may be associated with increased risk of cardiac, digital, and splanchnic ischemia, and clinical judgment should be used to determine situations in which a higher dose would be warranted.[6] The occurrence of 3 documented cases of digital ischemia in this study aligns with the incidence reported in the VASST trial,[4] although mean doses of vasopressin were higher in our study population. This suggests that a vasopressin dose of 0.04 units/min may be safe and effective, although our study was not specifically designed to investigate safety and effectiveness. Notably, the VANISH trial used a vasopressin dose of 0.06 units/min and reported a higher incidence of digital ischemia with no mortality benefit, which suggests that the potential risk may outweigh improvement in clinical outcomes, and should serve as a caution to clinicians considering a higher dose of vasopressin.[8] In the current study, the 3 patients with digital ischemia required mean doses of norepinephrine greater than 20 μg/min and had prolonged vasopressor infusions (greater than 72 h). Fortunately, there were no extravasation events in our study.

This study had several limitations. Although efforts were made to identify and discuss possible sources of confounding, such as the effects of multifactorial pathophysiological shock states (e.g., cardiogenic shock, hypovolemic shock), shifts in patient care goals, and differences in prescribing practices among clinicians, the interpretation of results is limited by the retrospective methodology. Lack of a control group limits our ability to assess causality and associations between findings, which would be hypothesis-generating for future research. The nature of the clinical environment may have led to incomplete documentation secondary to the complexity of data flowsheets, inconsistency in where information was recorded, or limited time for documentation because of high care demands of the critically ill population. Variability in documentation practices was observed both within and between clinician groups, potentially compromising the accuracy of our results. Finally, clinical decisions, such as initiation of renal replacement therapy or mechanical ventilation, were based on clinician expertise and patient-specific factors, and the observational nature of the data precludes any inference of correlations among medication therapy, disease progression, and adverse effects.

CONCLUSION

Vasopressin therapy in this study was largely comparable to its use in larger randomized controlled trials and the recommendations in guidelines[4,6,8]; however, variations in time to initiation, titration to discontinuation, and sequence of vasopressor discontinuation were evident. The variability in administration and discontinuation of vasopressin at our centre mimics the variability in the currently available literature guiding vasopressin use. The results of this study have been shared with clinicians and administrators in the study centre to allow further evaluation of routine practices. Although this study showed an effect of vasopressin in promoting hemodynamic stability and lowering norepinephrine requirements, the correlation of vasopressin therapy with improvement in clinical outcomes, such as mortality, remains unclear. Further studies are needed to determine the ideal approach to vasopressin use to ensure consistent clinical practices and optimal patient-centred outcomes. The main adverse events captured by our study were digital ischemia and post-discontinuation hypotension. Given the retrospective nature of the study, it was not possible to attribute other adverse reactions, such as cardiac ischemia and arrhythmia, to specific drug therapy.

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ON THE FRONT COVER

The Grotto, Bruce Peninsula National Park Tobermory, Ontario

Morgan Patrick took this photograph of The Grotto in Bruce Peninsula National Park using a Sony Alpha a6000 camera. The image was captured during a backcountry hiking trip along the Bruce Peninsula. Morgan is a fourth-year student in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta.

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.

Assessing the Need for Proton Pump Inhibitors for Patients Using Long-Term Nonsteroidal Anti-inflammatory Drugs without a History of Ulcers

Nonsteroidal anti-inflammatory drugs (NSAIDs) are toxic to the stomach. One proposed mechanism of this toxicity is a prostaglandin-mediated increase in gastric acid secretion.[1] If so, it would follow that increasing stomach pH, perhaps by means of an agent such as a proton pump inhibitor (PPI), would help to prevent ulcer complications secondary to NSAID use, such as bleeding and perforation. Clinical practice guidelines have recommended that patients at moderate risk (i.e., having at least one of the following factors: > 65 years old; receiving high-dose NSAID therapy; previous history of uncomplicated ulcers; or concurrent use of low-dose acetylsalicylic acid [ASA], corticosteroids, or anticoagulants) be given either cyclooxygenase-2 (COX-2) inhibitors alone or traditional nonselective NSAIDs plus misoprostol or a PPI.[2] The UpToDate clinical decision resource recommends PPIs as an option for reducing the risk of gastroduodenal toxicity and suggests that they may prevent ulcers in those who require NSAIDs.[3] We characterized the current evidence and determined the characteristics of patients to whom this evidence would apply.

We conducted a scoping search of the literature to identify a recently published systematic review of randomized controlled trials (RCTs) on this topic, and found 2 potentially suitable reviews.[4,5] The most recent systematic review, by Scally and others,[5] was unsuitable for our purposes because the authors did not report raw data for the trials included in their analysis. Instead, we examined the slightly older review, by Yang and others.[4] We did not look beyond the published data included within the systematic review. We focused specifically on RCTs that compared PPIs with placebo for patients receiving long-term NSAID therapy for pain; we did not consider trials of low-dose ASA. We collected information deemed relevant to our study question, specifically the types of outcomes and adverse events reported and the characteristics of included patients.

Yang and others[4] performed a meta-analysis of 15 RCTs to evaluate the "effectiveness and safety of PPIs" for "prevention of NSAID-associated serious ulcer complications". Six of the trials involved low-dose ASA, and 9 used NSAIDs for pain. We determined that the 9 NSAID trials, all of which were placebo-controlled, were relevant to our question. In terms of their study populations, 5 of the 9 included a mix of patients with and without a history of ulcers, and 3 included patients with previous ulcers; for 1 study, the population was unclear. Across the 9 trials, *Helicobacter pylori* status was highly variable: for 3 of the 9 trials, 100% of the patients tested negative; for 1 trial, 100% of the patients tested positive; for 4 trials, *H. pylori* status was mixed; and for 1 trial, *H. pylori* status was not reported. The following efficacy outcomes were reported: endoscopic ulcers (n = 7 trials), recurrent ulcer bleeding (n = 1 trial), and ulcer complications such as bleeding, perforation, or obstruction (n = 1 trial). In terms of safety outcomes, 3 of the 9 trials reported serious adverse events, 2 reported gastrointestinal (GI) bleeding, and 3 reported deaths. The authors concluded that "PPIs were significantly more effective than placebo in reducing ulcer complications (relative risk [RR] = 0.29; 95% confidence interval [CI], 0.20 to 0.42)".

An interesting finding was that the majority of trials reported on endoscopic ulcers as opposed to clinically important outcomes such as ulcer complications. The question of whether endoscopic ulcers lead to clinical ulcers is a point of contention, and there are opposing views on this issue in the current literature.[6,7] Because most of the identified evidence supporting PPIs in long-term NSAID use is based on their apparent influence on endoscopic ulcers,[8] it is important to determine whether a decrease in endoscopic ulcers is truly associated with a clinical reduction in ulcers or their subsequent complications.

Other independent risk factors besides long-term NSAID use may contribute to ulcer development. For example, it is believed that *H. pylori* infection plays a role in the occurrence of ulcers.[9] Several articles included in the review by Yang and others[4] involved patients who tested positive for *H. pylori* or had recently healed from the infection. It is unclear at this point whether PPIs are exerting their protective effects on NSAIDs or on other disease processes (e.g., *H. pylori* positivity).

We recognize that there is evidence showing an association between GI complications and NSAID use.[10,11] Patients should be made aware of these risks before starting short-term or long-term therapy. Our goal with this investigation was to ascertain whether PPIs are effective in mitigating the risk of GI complications. Overall, we found little evidence showing that PPI prophylaxis leads to fewer clinically important adverse outcomes in long-term NSAID users, especially those without a history of ulcer complications and those with no risk factors. Instead, we found that the trials included in the review by Yang and others[4] had the following common features: included patient populations with either a mixed or positive history of ulcers; mostly considered low-dose ASA to confer a GI risk similar to that of long-term NSAID use, which may not be true; and reported

on endoscopic outcomes as opposed to clinical ulcer complications. We realize that this evidence has some limitations, including the fact that the trials were of short duration and the fact that the risk of NSAID complications is cumulative over time. Some might suggest that there is a role for PPIs in preventing complications in long-term NSAID users who are at high risk of bleeding (e.g., those who test positive for *H. pylori*, have a history of ulcers, or are taking other GI-toxic medications), but we could not find any evidence to support this claim. We suggest that it may be appropriate to share this information with patients, specifically to address the uncertainties discussed here and especially with the knowledge that long-term PPI use may increase the risks of bone disease, infection, and other harms.[12,13]

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Practical Guidance in Perioperative Management of Immunosuppressive Therapy for Rheumatology Patients Undergoing Elective Surgery

Michelle Boyce and Anne Massicotte

INTRODUCTION

Surgical site infections are an important cause of prolonged hospitalization, with an associated mortality rate of 3%.[1] The incidence of a surgical site infection after surgery is 2% to 5%, and among surgical patients, such infections are the most common type of health care–associated infection.[2] Patients who are receiving immunosuppressive therapy may be at increased risk of a postsurgical infection and delayed wound healing.[3] In addition, multiple other contributing factors may increase the risk of infection after surgery, including (but not limited to) prolonged surgery (> 2 h), advanced age, obesity, smoking, cancer, other immunocompromising conditions, diabetes, and abdominal surgery.[4] The risk of infection depends on whether the surgery is performed in a clean, sterile environment and considered low risk (e.g., cataract surgery, arthroscopy), or the surgery is performed in a contaminated, dirty environment and considered high risk (e.g., abdominal or gastrointestinal surgery).[3,5] Furthermore, the type of surgical wound may be classified as clean, clean-contaminated, contaminated, and dirty/infected, as defined by the US Centers for Disease Control and Prevention,[1] with each classification associated with a different degree of risk for a surgical site infection.[4] At the same time, the severity of the patient's underlying disease is an important factor to consider when determining perioperative drug management.[6] For example, if the disease is severe, holding immunosuppressants may result in a negative outcome, such as a disease flare or relapse, whereas a patient with mild disease may tolerate temporary discontinuation of therapy. Hence, a risk–benefit assessment for each patient is warranted.[6,7]

This article aims to provide guidance to clinical practitioners for the perioperative management of rheumatology patients who are receiving immunosuppressive therapy and for whom elective surgery is planned. This guidance is a collection of recommendations from national rheumatology associations and other groups of rheumatology specialists. For the purpose of this review, immunosuppressive therapy includes common traditional disease-modifying antirheumatic drugs, as well as biologic agents used for rheumatoid diseases.

METHODS

A formal literature search in Ovid MEDLINE and PubMed was conducted to gather relevant articles. The search terms, either as MESH words or keywords, were disease modifying antirheumatic drug*, DMARD*, immunosuppressive agents, biologic*, monoclonal antibodies, tumor necrosis factor-alpha, rheumatic diseases, practice guideline*, recommendation*, consensus, surgical procedures, surgery, and operative (peri, pre, intra, post). Searches were limited to guidelines and review articles addressing the perioperative use of immunosuppressants. A general Google search was also performed to capture other possibly relevant material that would not have been formally indexed. After removal of duplicates, irrelevant articles (i.e., those that did not substantially address our topic), and articles written in languages other than French or English, 4 national guidelines and 4 review articles remained as the best available evidence. Most of the data that we reviewed focused on patients with rheumatic diseases, and we therefore limited this guidance document to this patient population.

RESULTS

The literature search revealed a lack of prospective studies establishing the optimal withhold and restart times for immuno-

suppressants during the perioperative period. As such, the recommendations and reviews retrieved through the literature search focused on guiding principles (e.g., type of surgery, drug half-life, and drug dosing interval).

Table 1 summarizes management recommendations for rheumatology patients during the perioperative period of elective surgeries for common immunosuppressants marketed in Canada.[3,5-14] Canadian recommendations have been prioritized as much as possible (in Table 1, see the recommendations originating from reference 3). The information in this table applies only to rheumatology patients and does not cover other populations, such as transplant patients, who may be at risk of organ rejection if immunosuppressive therapy is stopped temporarily.

The table separates "all surgeries" from "total hip and total knee arthroplasty" for the following 2 reasons: first, the references cited in these 2 categories adopted a very different approach for the perioperative management of immunosuppressants, and second, the US recommendations are specific to patients undergoing elective total hip or total knee arthroplasty. The table also provides, in many cases, 2 different options for "all surgeries" (i.e., not limited to a specific type of surgery), reflecting the lack of consensus on the perioperative management of immunosuppressants.

When determining the period for which a drug should be held before surgery, the elimination half-life ($t_{1/2}$) of each immunosuppressant and its metabolites is a useful tool.[3,5,14] Most of the guidelines recommend holding a drug for 2 to 3 half-lives if the surgery carries a low risk of infection, and for 5 half-lives if the surgery carries a high risk of infection.[3,5] In Table 1, the minimum of 2 (or in some cases 3) half-lives and maximum of 5 half-lives are stated with the actual calculated time in parentheses for each drug; if there is a range of half-lives, the range of time to hold the drug is stated. The reported half-life of a particular drug may differ among sources in the literature, and therefore the time to hold the drug, as stated in Table 1, may differ slightly from the quoted references. Clinical judgment will be of primary importance when applying these recommendations to special populations such as elderly patients and those with renal or hepatic impairment, given likely differences in pharmacokinetic parameters.

In the context of total hip and total knee arthroplasty, the recommendations in the US guidelines are based on the drug dosing interval rather than drug half-life, because the half-life does not always correlate with each drug's duration of action.[9] The US recommendation is to schedule the surgery at the end the drug dosing interval, when it would normally be the time to proceed with the next dose.[9]

In addition to the type of surgery, drug half-life, and drug dosing interval, addressed in Table 1, the final decision about the exact duration of drug-holding should still be individualized according to patient-specific risk factors and comorbidities.

Before restarting an immunosuppressant postoperatively, evaluation of the wound is important to ensure adequate healing, because re-initiation of immunosuppressive therapy too early can put the patient at increased risk of postoperative infection. Most of the available guidelines recommend resuming the immunosuppressive therapy when there are no signs of infection and there is evidence of satisfactory wound healing.[3,5,14]

HYPOTHETICAL CASE STUDIES: APPLICATION OF PRACTICAL GUIDANCE

Case 1

A 34-year-old woman with breast cancer is scheduled to undergo an elective mastectomy. She has rheumatoid arthritis that has been well controlled over the past 2 years with adalimumab 40 mg SC every 2 weeks and methotrexate 7.5 mg orally once weekly. She has no renal or hepatic impairment. Using Table 1 as a guide, we could recommend holding the adalimumab for 28 days before surgery (given that a mastectomy is generally classified as a clean surgical procedure) and continuing the methotrexate throughout the perioperative period. The patient could resume adalimumab therapy when there is no evidence of infection and wound healing is satisfactory.

Case 2

A 60-year-old man with psoriatic arthritis receives infliximab by infusion every 4 weeks, with his most recent infusion administered on March 2. The patient has responded well to infliximab and has not experienced any flares of his disease in the past year. He is scheduled to undergo an elective total hip arthroplasty. The orthopedic surgeon is wondering for how long the infliximab should be held before the surgery. According to Table 1, it would be best to schedule the surgery during the week of March 30 (at the end of the infliximab dosing interval, i.e., during week 5) and to hold the dose scheduled for March 30. The patient could resume his infliximab infusions at least 14 days after surgery, when there is no evidence of infection and wound healing is satisfactory.

CONCLUSION

Patients who are receiving immunosuppressive therapy may be at increased risk of infection after surgery; therefore, holding immunosuppressants may be warranted in the perioperative period. However, holding immunosuppressants may result in a flare of the underlying disease. This review has summarized practical guidance addressing this issue for rheumatology patients. Table 1 is provided as a guide in the decision-making process, but final decisions should be tailored to each patient, balancing the risks and benefits of holding or continuing therapy. Factors to consider when deciding to continue or hold an immunosuppressant drug include the type of surgery, comorbidities, severity of the disease, and any other factor that could contribute to the

Table 1 (part 1 of 4). Perioperative Management of Immunosuppressive Therapy for Adult Rheumatology Patients*

Generic Name and Approved Indications†[8]	Approved Dosage†[8]	Half-life ($t_{1/2}$)[8,12,13]	Perioperative Recommendations	
			Preoperative	**Postoperative**
Abatacept Psoriatic arthritis, rheumatoid arthritis	500–1000 mg IV q4weeks 125 mg SC once weekly	13–14 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (26–28 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (65–70 days) *All surgeries, option 2*[10] Hold for 25 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 2 or 5)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Adalimumab Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis	40 mg SC q2weeks	14 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (28 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (70 days) *All surgeries, option 2*[10] Hold for 30 days	*All surgeries*[3,5] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 2 or 3)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Anakinra Rheumatoid arthritis	100 mg SC daily	4–6 h	*All surgeries, option 1*[10] Hold for 1–2 days before surgery *All surgeries, option 2*[11] Hold for the week of surgery	*All surgeries*[11] Restart 1–2 weeks after the procedure
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during day 2)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Azathioprine Rheumatoid arthritis May be used clinically for SLE (not approved by Health Canada)	Rheumatoid arthritis: 1–2.5 mg/kg IV or PO per day SLE: Not applicable	2–5 h	*All surgeries, option 1*[7,10] Continue, do not hold *All surgeries, option 2*[11] Hold for 1 day before surgery	*All surgeries*[11] If held, restart 3 days after procedure
			Total hip and total knee arthroplasty[9] Severe SLE: Continue, do not hold Not-severe SLE: Hold for 1 week before surgery	*Total hip and total knee arthroplasty*[9] Severe SLE: Not applicable Not-severe SLE: Restart 3–5 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Belimumab SLE	10 mg/kg IV q4weeks 200 mg SC weekly	18–19 days	*All surgeries* No recommendation stated	*All surgeries* No recommendation stated
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 5) NOTE: The guideline does not address patients on an SC weekly regimen; in this case, scheduling the surgery at the end of the dosing interval, i.e., during week 2, is a reasonable option.	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory

continued on page 221

Table 1 (part 2 of 4). Perioperative Management of Immunosuppressive Therapy for Adult Rheumatology Patients*

Generic Name and Approved Indications†[8]	Approved Dosage†[8]	Half-life ($t_{1/2}$)[8,12,13]	Perioperative Recommendations	
			Preoperative	Postoperative
Certolizumab pegol Ankylosing spondylitis, nr-Ax SpA, psoriatic arthritis, rheumatoid arthritis	200 mg SC q2weeks 400 mg SC q4weeks	14 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (28 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (70 days) *All surgeries, option 2*[10] Hold for 28 days	*All surgeries*[3,5] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 3 or 5)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Cyclosporine Rheumatoid arthritis May be used clinically for SLE (not approved by Health Canada)	Rheumatoid arthritis: 1.25–2.5 mg/kg PO q12h SLE: Not applicable	8–19 h	*All surgeries*[7,10] Hold for 1 week before surgery	*All surgeries*[10] Restart 1 week after surgery
			Total hip and total knee arthroplasty[9] Severe SLE: Continue, do not hold Not-severe SLE: Hold for 1 week before surgery	*Total hip and total knee arthroplasty*[9] Severe SLE: Not applicable Not-severe SLE: Restart 3–5 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Etanercept Active arthritis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis	50 mg SC weekly 25 mg SC twice weekly	102 h	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (9 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (21 days) *All surgeries, option 2*[10] Hold for 10 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 2)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Golimumab Ankylosing spondylitis (SC/IV), Nr-Ax SpA (SC), psoriatic arthritis (SC/IV), rheumatoid arthritis (SC/IV)	50 mg SC q4weeks 2 mg/kg IV q8weeks	14 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (28 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (70 days) *All surgeries, option 2*[10] Hold for 28 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 5 or 9)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Hydroxychloroquine Lupus erythematosus, rheumatoid arthritis	200–400 mg PO daily	40 days	*All surgeries*[6,7,10,11] Continue, do not hold	*All surgeries* Not applicable
			Total hip and total knee arthroplasty[9] Continue, do not hold	*Total hip and total knee arthroplasty*[9] Not applicable
Infliximab Active arthritis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis	3–10 mg/kg IV q4–8weeks	7–15 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (14–30 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (35–75 days) *All surgeries, option 2*[10] Hold for 19 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 5, 7, or 9)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory

continued on page 222

Table 1 (part 3 of 4). Perioperative Management of Immunosuppressive Therapy for Adult Rheumatology Patients*

Generic Name and Approved Indications†[8]	Approved Dosage†[8]	Half-life ($t_{1/2}$)[8,12,13]	Perioperative Recommendations	
			Preoperative	Postoperative
Leflunomide Rheumatoid arthritis	10–20 mg PO daily	14–19 days; may be prolonged because of enterohepatic recycling	*All surgeries, option 1*[7] Hold for 1 week before, and do a cholestyramine washout§ *All surgeries, option 2*[10,11] Hold for 2 weeks	*All surgeries*[10,11] Restart 3 days after procedure
			Total hip and total knee arthroplasty[9] Continue, do not hold	*Total hip and total knee arthroplasty*[9] Not applicable
Methotrexate Psoriatic arthritis, rheumatoid arthritis	Psoriatic arthritis: SC/IM/IV, 10–25 mg per week PO, 7.5–25 mg per week Rheumatoid arthritis: SC/IM/IV/PO, 7.5–20 mg per week	3–10 h	*All surgeries, option 1*[3,5,7,10] Continue, do not hold *All surgeries, option 2*[6,10,11] Hold for 1 week before **only in exceptional situations** (e.g., complex surgery; significant kidney, liver, or lung disease; high-dose steroids; uncontrolled diabetes mellitus)	*All surgeries*[6] If stopped before procedure, restart the week after surgery if there is no clinical infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Continue, do not hold	*Total hip and total knee arthroplasty*[9] Not applicable
Mycophenolate mofetil and sodium/acid No rheumatology indications approved by Health Canada; may be used clinically for SLE	Not applicable	8–18 h	*All surgeries*[10] Hold for 1 week before surgery	*All surgeries*[10] Restart 1–2 weeks after surgery
			Total hip and total knee arthroplasty[9] Severe SLE: Continue, do not hold Not-severe SLE: Hold for 1 week before surgery	*Total hip and total knee arthroplasty*[9] Severe SLE: Not applicable Not-severe SLE: Restart 3–5 days after surgery when there is no evidence of infection, and wound healing is satisfactory
Rituximab Rheumatoid arthritis	1000 mg IV q2weeks × 2 doses NOTE: Course to be repeated q16–24weeks as needed	18 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (36 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (90 days) *All surgeries, option 2*[10] Hold for 100 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing cycle (during month 7)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Secukinumab Ankylosing spondylitis, psoriatic arthritis	150–300 mg SC monthly	22–31 days	*All surgeries* Clean surgery‡[5]: Hold for 3 × $t_{1/2}$ (66–93 days) Contaminated/dirty surgery[5]: Hold for 5 × $t_{1/2}$ (110–155 days)	*All surgeries*[5] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 5)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Sulfasalazine Rheumatoid arthritis	1000 mg twice daily	8–15 h	*All surgeries, option 1*[11] Hold for 1 day before surgery *All surgeries, option 2*[6] Continue, do not hold, **unless** potential drug interaction or concern of hepatotoxicity, in which case a hold for 2 days is recommended	*All surgeries*[6,11] If held, restart 3 days after procedure or when clinically stable
			Total hip and total knee arthroplasty[9] Continue, do not hold	*Total hip and total knee arthroplasty*[9] Not applicable

continued on page 223

Table 1 (part 4 of 4). Perioperative Management of Immunosuppressive Therapy for Adult Rheumatology Patients*

Generic Name and Approved Indications†[8]	Approved Dosage†[8]	Half-life ($t_{1/2}$)[8,12,13]	Perioperative Recommendations	
			Preoperative	Postoperative
Tacrolimus Rheumatoid arthritis (PO only) May be used clinically for SLE (not approved by Health Canada)	Rheumatoid arthritis: IR, 3 mg PO once daily SLE: Not applicable	PO, IR: 9–36 h	*All surgeries* No recommendation stated	*All surgeries* No recommendation stated
			Total hip and total knee arthroplasty[9] Severe SLE: Continue, do not hold Not-severe SLE: Hold for 1 week before surgery	*Total hip and total knee arthroplasty*[9] Severe SLE: Not applicable Not-severe SLE: Restart 3–5 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Tocilizumab Rheumatoid arthritis (IV/SC)	4–8 mg/kg IV q4weeks 162 mg SC q1–2weeks	IV: 11–13 days SC: 5–13 days	*All surgeries, option 1* Clean surgery‡[3]: Hold for 2 × $t_{1/2}$ (IV: 22–26 days; SC: 10–26 days) Contaminated/dirty surgery[3,5]: Hold for 5 × $t_{1/2}$ (IV: 55–65 days; SC: 25–65 days) *All surgeries, option 2*[10] Hold for 26 days	*All surgeries*[3,5,14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 2 or 5)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Tofacitinib Psoriatic arthritis, rheumatoid arthritis	IR: 5 mg twice daily ER: 11 mg once daily	IR: 3 h ER: 6 h	*All surgeries*[14] Hold for 5 × $t_{1/2}$ (IR: 15 h; ER: 30 h)	*All surgeries*[14] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery 7 days after last dose	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory
Ustekinumab Psoriatic arthritis (SC)	45–90 mg SC q12weeks	15–46 days	*All surgeries* Clean surgery‡[5]: Hold for 3 × $t_{1/2}$ (45–138 days) Contaminated/dirty surgery[5]: Hold for 5 × $t_{1/2}$ (75–230 days)	*All surgeries*[5] Restart when there is no evidence of infection, and wound healing is satisfactory
			Total hip and total knee arthroplasty[9] Schedule surgery at the end of the dosing interval (during week 13)	*Total hip and total knee arthroplasty*[9] Restart at least 14 days after surgery, when there is no evidence of infection, and wound healing is satisfactory

ER = extended release, IM = intramuscular, IR = immediate release, IV = intravenous, nr-Ax SpA = nonradiographic axial spondyloarthritis, PO = by mouth (oral), SC = subcutaneous, SLE = systemic lupus erythematosus.
*Decision should always be individualized on the basis of clinical judgment and assessment of clinical factors.
†Approval by Health Canada, for adult patients with rheumatology conditions.
‡If bloodless surgery such as cataract, the UK National Health Service suggests to continue drug.[5]
§Administer 8 g of cholestyramine 3 times daily for 11 days to rapidly reduce leflunomide plasma levels.[8]

patient's risk of infection.[3] If it is decided to hold the drug before surgery, a general guide of holding the drug for 2 to 5 half-lives may be used, unless the planned surgery is an elective total hip or total knee arthroplasty, for which use of the dosing-interval method is suggested. There is a general consensus that immunosuppressive therapy should be resumed when there is no evidence of infection and wound healing is satisfactory. Because clinical data and guidelines are few, there is a need for further research to develop a standardized approach for optimizing perioperative care of these patients.[6,7]

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Recognition of Advanced Practice Pharmacists in Australia and Beyond: Considerations for Canadian Practitioners

Rochelle M Gellatly and Kirsten Galbraith

INTRODUCTION

The concept of advanced pharmacy practice has been of national and international interest for many years as a means to address increases in patient complexity and changes in health care systems. Comorbidities are often considered as a factor in complexity, and the prevalence of Canadians and Australians living with 2 or more comorbidities is rising.[1-3] More than two-thirds (65.7%) of Canadian seniors and more than one-third (36.1%) of Australian seniors take at least 5 different prescription medications, further adding to their complexity.[4,5]

In 2019, it was predicted that Canada would spend approximately $264.4 billion on health care ($7068 per resident), with the cost of medications making up the third-largest portion of this expenditure.[6] Australia is also facing significant challenges in its health care system, with per capita health care expenditures similar to those in Canada.[7] With these increasing costs and patient complexity, there is demand for pharmacists to develop a more advanced practice, one that extends beyond entry to the profession.[8] This demand has been recognized by the Australian pharmacy profession and has led to the development and implementation of the Advanced Pharmacy Practice Framework (APPF).[9]

The *Canadian Journal of Hospital Pharmacy*'s Advanced Pharmacist Practitioner Series, of which this article is a part, aims to engage readers with this topic as a means of inspiring action to optimize pharmacy practice, addressing both the gaps in the Canadian health care system and the needs of patients. Furthermore, a report from the Pharmacy Thought Leadership Summit, held in 2016, identified advanced practice as part of the solution to optimize pharmacy practice in Canada.[10] This solution includes clearly defining advanced practice and specialization, as well as developing a national certification and formal recognition process for specialty and advanced practice. The aim of this article is to describe the Australian approach to recognizing advanced pharmacy practice, the global development of advanced practice, and considerations for the Canadian pharmacy profession in adopting a formal recognition process.

BACKGROUND

Development of the APPF

The first steps for the Australian pharmacy profession were to define advanced practice and develop a framework outlining such a practice. The APPF, released in 2012, described advanced practice as "practice that is so significantly different from that achieved at initial registration that it warrants recognition by professional peers and the public of the expertise of the practitioner and the education, training and experience from which that capability was derived."[9]

All pharmacy bodies in Australia collaborated on the APPF, which describes 30 competencies across the 5 domains of professionalism and ethics, communication and collaboration, medicines management and patient care, leadership and management, and education and research.[9] The competencies within the domains are mapped against 3 stages of performance (Table 1).[11] The APPF drew from pre-existing frameworks in Australia with focused scopes of practice, as well as the domains in the UK Competency Development and Evaluation Group's Advanced and Consultant Level Competency Framework.[9,12] Not only was

Table 1. Advancing Practice Credentialing Stages[11]

Stage	Definition	Credential
Stage I Advancing Practice	Performing at a stage of advancement beyond early years of practice.	AdvPP(I)
Stage II Advancing Practice	An experienced and recognized local leader with proven expertise in an area of practice and capable of consistently managing complex situations.	AdvPP(II)
Advanced Practice Pharmacist	A nationally and/or internationally recognized leader with a breadth of experience and expertise.	AdvPracPharm

the APPF developed to assist the profession in meeting the changing health care needs of Australians, it was also recognized as a tool for assuring the public of the competence and safety of advanced pharmacists.[12]

In 2015, a Credentialing of Advanced Practice Pharmacists pilot program was undertaken.[13] Candidates submitted professional practice portfolios consisting of evidence of accomplishments with context and impact statements, mapped against the 3 stages of the 30 advanced practice competencies.[9] During the pilot program, trained evaluators examined 43 portfolios with reference to the APPF competencies to establish practitioner performance. Twenty-eight pharmacists were recognized as "Advanced Practice Pharmacists" and agreed to have their names listed on a public website.[14] The pilot program demonstrated that the framework was adaptable and relevant to evaluate performance in all areas of pharmacy practice.[15] The APPF has since been integrated into Australia's National Competency Standards Framework for Pharmacists (NCSFP).[16] This document now serves as the framework to describe a pharmacist's performance and development goals at any stage of their career.

Canadian and Australian Health Care and Pharmacy Practice

To further contextualize the discussion of advancing practice, it is important to understand the Australian health care system and pharmacy practice. Moles and Stehlik[17] have previously completed a comprehensive review. The Australian health care system is funded both publicly and privately. Australia's Medicare program provides nationally subsidized primary care and publicly funded treatment in public hospitals.[17] Private health insurance covers private hospitalizations and other health care–related services and items. In Canada, the medicare system is publicly funded.[18] Both Australia and Canada have subsidized medicines programs; Canada's is delivered at the provincial or territorial level, whereas Australia's is delivered nationally.[17,18]

The pharmacist density in Australia and Canada is similar (Australia with 12.59 and Canada with 11.74 pharmacists per 10 000 population).[19] Most pharmacists work in community practice (63% in Australia versus 70% in Canada), with a smaller proportion practising in hospitals (18% in Australia versus 15% in Canada), followed by other sectors including education, industry, and government.[20,21] Aligned with Canadian practice, Australian pharmacists within hospital and community settings deliver dispensing and patient-centred clinical pharmacy services. Recently, the Society of Hospital Pharmacists of Australia established a national Foundation Residency Program, and it is developing Advanced Training Residencies.[22] These experiential programs are aligned with the NCSFP and are similar in scope to the Canadian postgraduate year 1 and year 2 residency programs, respectively.[16] Programs in both countries provide a professional linkage that engages the future workforce in recognition of their professional capabilities; the Australian programs are more overtly linked to recognition of advancing practice.

CURRENT STATE

Advanced Practice Recognition in Australia

After the successful piloting of advanced practice credentialing, the program now operates under the formalized banner of "Advancing Practice", and the first round of credentialing opened in March 2018.[23] Using the NCSFP, this credentialing program recognizes pharmacists at all stages of advancement (Table 1).[16] All pharmacists can undertake career mapping to identify areas of strength and improvement, which encourages professional development and progression for the purposes of delivering better health care to Australians. Since March 2018, more than 60 pharmacy practitioners have been recognized according to the 3 stages of advancement.[24]

Portfolio Submission

A portfolio is a "formal documentation of training, achievements and experience".[25] It is an accepted evaluation method used to provide evidence of competencies, including professional behaviour, practice-based improvements, research activities, and professional experience.[25]

As part of the Advancing Practice application, the submission of a portfolio is required. The portfolio addresses the 5 competency domains, which are representative of key elements of pharmacy practice and are skills that are also seen in Canadian pharmacists. Furthermore, the portfolio is made up of written

statements, with supporting evidence, that demonstrate the applicant's stage of performance and impact of their work for each competency. The portfolio is reviewed by 2 experienced and trained pharmacists for independent evaluation and feedback. A portfolio-building guide is available to support applicants and to describe the criteria for portfolio evaluation and credentialing.[26]

The practice of self-reflection and evaluation that occurs during portfolio building further serves to identify areas for career advancement and professional development. Notably, reflective practice portfolios are required for documenting continuing professional development for ongoing registration as a pharmacist in both Canada and Australia.[27-30]

Advancing Practice in Education

The advancing practice agenda in Australia remains relatively new, so it has been imperative to raise the profile of the benefits of the credentialing pathway and of working toward more advanced practice. Educators have an important role in helping move the profession away from focusing on a record of professional education, to a more reflective approach of life-long learning, including maintenance of a portfolio. Universities are incorporating portfolio-based assessments that include elements of continuing professional development into their undergraduate and postgraduate studies.[31] For example, Monash University in Melbourne, Australia, has incorporated a capstone unit (Professional Practice Portfolio) in the Master of Clinical Pharmacy degree. Students develop a portfolio consistent with the Advancing Practice portfolio-building guide, collating evidence from their educational units and workplace experience and mapping it against the NCSFP. They obtain experience writing context and impact statements, and their portfolios are independently evaluated, often by Advanced Practice Pharmacists. In the undergraduate (entry-to-practice) program at Monash University, reflective practice is incorporated into the curriculum. Students write regular skills-based reflections and develop personalized learning plans, then receive individualized feedback. This activity prepares graduates for the need to maintain a portfolio from day 1 of practice.

Current Challenges with Definitions of Advanced Practice and Specialization

A key means of developing an advanced practice framework, as noted by the Australian experience, is having clear definitions of advanced practice and specialization. A 2015 report describing advanced practice and specialization in pharmacy noted that the definitions and understanding of these 2 terms varied greatly throughout the world.[8] This variation was echoed by the Needs Assessment of Specialization in Pharmacy in Canada, which noted that the definitions of advanced practice and specialization are critical to establishing formal recognition of pharmacists.[32] Without clear definitions, there may be confusion among the profession, the public, and other health practitioners. Furthermore, the variation in definitions has created challenges in obtaining international harmony across the profession for the purposes of implementing frameworks for advanced practice recognition. In response to this problem, Australia's NCSFP uses scope of practice and performance level to describe the differences between specialty and advanced practice, respectively (Figure 1).[16,33] Advanced practice generally refers to a higher level of performance, whereas specialty practice refers to a narrower, focused scope of practice.

In defining advanced pharmacist practice, the Needs Assessment of Specialization in Pharmacy in Canada adopted the APPF's definition of advanced practice.[9,32] Although the Needs Assessment recognized the importance of distinguishing between advanced pharmacist practice and specialty practice, it did include components of advanced practice within its definition of pharmacist specialists. It defined pharmacist specialists as pharmacists who " maintain an active clinical practice that is limited to a particular type of patients …, part of the body …, or location of practice. … Pharmacy specialization requires an advanced body of knowledge distinct of the general practitioner and a specialized or enhanced depth of competency including knowledge, skills, attitudes and accountabilities based on the physical, social, and health sciences, sufficient to manage the most complex of cases and provide clinical leadership in the field."[32] Despite the lengthy definition of pharmacist specialists used in the Needs Assessment, there are clearly elements of the Australian definition of advanced practice embedded within it. Both definitions highlight that advanced competencies are required, extending beyond just knowledge. Limitations of the definitions of advanced pharmacy practice and pharmacist specialists in the Needs Assessment include the potential confusion created by overlapping definitions, as well as the fact that pharmacist specialists appear to include clinical practitioners only.

Of note, some jurisdictions in Canada have job roles titled "Clinical Pharmacy Specialist", which generally relate to pharmacists with higher qualification, working in particular areas of focus. Likewise, some Australian settings have job roles that include the word "advanced". In both cases these terms are related to job titles rather than specific credentials for nominated pharmacists, further adding to the confusion of how a pharmacist specialist or advanced practice pharmacist would be identified. Credentialing of advanced practice is recognition of an individual pharmacist's performance, rather than the job in which they are employed.

EVIDENCE

Impact on Clinical Outcomes

The clinical skills of advanced pharmacy practitioners are acknowledged to be at higher levels than those of entry-level pharmacists.[8] Unfortunately, because of the varying definitions of

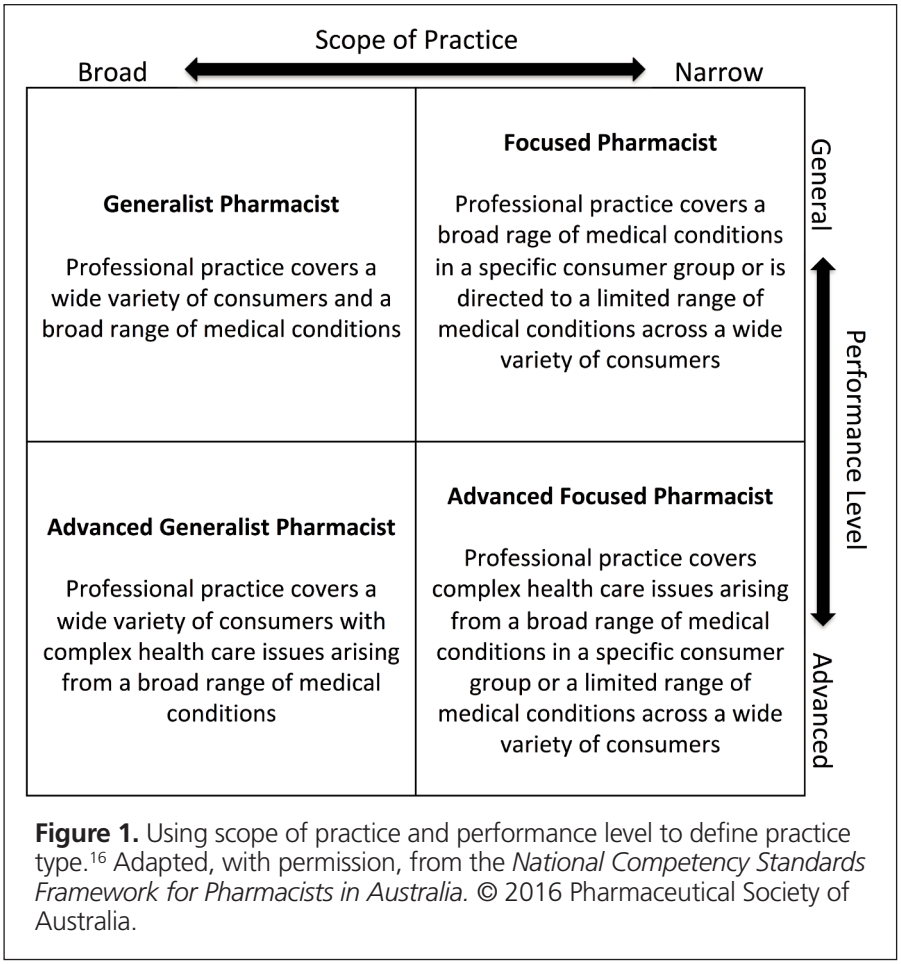

Figure 1. Using scope of practice and performance level to define practice type.[16] Adapted, with permission, from the *National Competency Standards Framework for Pharmacists in Australia.* © 2016 Pharmaceutical Society of Australia.

advanced and specialty practice used internationally, there are challenges in demonstrating the clinical impact of advanced practice pharmacists. Several studies of pharmacists working in specialized, focused roles have reported associated positive patient outcomes and cost savings.[34-37] Unfortunately, these studies have not elaborated on the depth and breadth of the pharmacists' experience. To achieve recognition as an Advanced Practice Pharmacist in Australia, candidates must demonstrate their impact. In many cases, this impact includes changing practice, contributing to knowledge gaps via publication, and other activities known to have an impact on clinical outcomes. How we can more formally evaluate the impact of advanced practice on patient outcomes, beyond an individual or a small group basis, will be a challenge for the profession to address.

Australian and Canadian Perspectives on Advanced Practice

A survey of Australian pharmacists conducted by Jackson and others[38] in 2013, showed that 66% (114 respondents) self-identified as working at an advanced level of practice and a further 20% (34 respondents) identified as working toward advanced practice. However, it appeared that respondents did not understand that the advancing practice competencies extend beyond knowledge and also encompass communication, teamwork, professional leadership, education, and research. This result suggested a need to build awareness and understanding within the profession of the scope of advanced practice within the framework. This conclusion was reinforced by the finding that, of those pharmacists who considered they had been formally assessed as being advanced practitioners, many cited agencies that grant recognition on the basis of an assessment of knowledge or process, which would be insufficient for demonstrating advanced practice under the APPF.

A survey of Canadian pharmacists found that 48% of the 2084 respondents self-identified as a pharmacist specialist, as defined by the Needs Assessment of Specialization in Pharmacy in Canada.[32] Furthermore, a survey conducted by the Canadian Society of Hospital Pharmacists (CSHP) in 2017 showed that 57% (114/199) of respondents reported working in an advanced practice role.[39] It should be noted that the definition of an advanced practice role in the CSHP survey differed from the definitions used by the APPF and the Needs Assessment of Specialization in Pharmacy in Canada.

Consistent with findings from the United Kingdom, the survey by Jackson and others[38] also revealed that Australian pharmacists preferred the submission of a professional portfolio for assessment of advanced practice. Interestingly, these respondents were not in favour of evaluation by a written examination, aligned with other international viewpoints.[38] Although at the time the second-highest preference for assessment method was "recognition of a prior qualification", it was decided that this would not be accepted as the sole piece of evidence required for credentialing as an advanced practitioner.[38] Many applicants with a post-graduate qualification feature aspects of their degree as evidence in their portfolio, mapped against relevant competencies.

In the Canadian survey, the preferred method of certification was not explored; however, respondents were directly asked about their preferences for recertification via written examination, of which the majority were in favour.[32] It is unclear how the skills that extend beyond knowledge could be evaluated in this format.

International Perspectives on Advanced Practice

The International Pharmaceutical Federation's (FIP's) *Advanced Practice and Specialisation in Pharmacy Global Report 2015* collated information provided by participant countries regarding advanced and specialty practice around the world.[8] The lack of a standard definition for advanced or specialty practice affected the information provided by the respondents. Eleven of the 17 countries that responded reported the availability of professional recognition of advanced practice and/or specialization. Professional recognition was offered in a number of forms, including formal credentials, protected titles and postnominal titles, a separate register, career progression tracks, and financial incentives. Formal credentialing was the standard professional recognition mechanism shared across the countries. Certification requirements were different in every case study and were typically a combination of examinations; peer reviews; postgraduate qualifications, certificates, or training courses; portfolio assessments; work experience; specialty residency programs; internships; work-related theses; and scope of practice evidence.

Applicability of Frameworks Globally

The FIP report also demonstrated that despite some differences in pharmacy practice, there are several practice-related competencies with global applicability.[8] The practice similarities between Canada and Australia are suggestive of this broad applicability. Work conducted by Udoh and others[40,41] has shown that both content experts and practitioners across the globe found the advanced practice competencies of the UK's Royal Pharmaceutical Society Advanced Pharmacy Framework[42] and the Australian APPF to be similar. These results support the notion of practice-related competencies with global relevance.

Published case studies indicate that the advanced and specialty frameworks of some countries are adopted and adapted from another country or profession.[43,44] In addition to Australia's adaptation of the Competency Development and Evaluation Group's Advanced and Consultant Level Competency Framework, Singapore's specialist accreditation framework for pharmacists was developed in line with that country's medical and dental specialization frameworks.[8]

Building on the concept of global similarities in pharmacy practice, the FIP Global Advanced Development Framework was launched in September 2019.[45] This framework is a validated tool to support professional development and recognition of the pharmacy workforce internationally. It maps 3 advanced practice stages across the following developmental competencies: "medicines expertise, leadership capabilities …, managing health and professional delivery services and people, training and mentoring, and developing evaluation skills and innovation in health and professional service provision".[45]

FUTURE DIRECTIONS

Learnings from Australia

Engaging all pharmacy-related member organizations has been imperative to the successful implementation of a framework for advanced practice in Australia. Embedding the framework in the NCSFP and embedding reflective learning into education have also been instrumental in engaging the profession.[16] At the same time, there have been numerous challenges in the credentialing system, largely relating to sustainability. Despite the survey results of Jackson and others,[38] the perception among some pharmacists is that Advancing Practice is relevant to only a very small number within the profession, so many have not yet engaged in the process. Some sectors lack obvious drivers for pharmacists to pursue formal recognition of more advanced practice, such as links to career progression, remuneration, and employer expectations; however, this situation may be changing. Recently the Pharmaceutical Society of Australia released its *Pharmacists in 2023* report, describing the changes needed to deliver safety and quality in the use of medicines.[46] An accompanying report describes roles and remuneration and clearly links new roles for pharmacists exhibiting more advanced practice.[47] It is expected this initiative will further acknowledge the importance of pharmacists demonstrating their level of performance. In addition, some hospitals now have well-described career progression pathways mirroring the advancement initially recognized by the APPF.[48]

Advanced Practice in Canada

In the previously described *Advanced Practice and Specialisation in Pharmacy Global Report 2015*,[8] the Canadian respondents made it clear that agreed definitions of advanced and specialty practice addressing practice scope, competencies, and

responsibilities are important for pharmacists and other health care professionals. They reported that developing a "funding model" is important for planning a sustainable credentialing system in Canada. These respondents also recognized that the push for pharmacists' specialization must be based on improvements to patient care and within health systems. They also reported that pharmacists endorse the development of Canadian-specific accreditation programs for specialization but recognize that using international certification bodies might be a viable and sustainable option, considering the size of Canada's pharmaceutical workforce.[8] Given the limitations associated with relying solely on exam-based credentialing, which has a strong focus on demonstrating knowledge rather than impact, it may be worth the profession in Canada reconsidering this option.

The system and processes in place in Australia and the United Kingdom are similar and reproducible and have been demonstrated to be comparable. Given the similarities in health care systems, workforce size, and practice scope, adaptation of an international credentialing system, as demonstrated in Australia and elsewhere, may be feasible in Canada.

CONCLUSION

To further optimize patient care within the Canadian health system, we require pharmacists to be working at a more advanced level. Formal recognition of advanced practice and support for progression of pharmacists through the use of a competency framework in Canada could assist in this endeavour. Australia has established a comprehensive framework and credentialing system that, given the similarities between the Canadian and Australian workforces and health care systems, could be adapted to the Canadian setting.

Many Canadian pharmacists perceive themselves as practising at a level that is beyond entry-to-practice. Building on the work that has already commenced in Canada, Australia, and beyond, an opportunity exists now to unite the profession and more formally recognize the contribution of the Canadian workforce. Furthermore, as advanced practice progresses across the globe, it is imperative that the profession begin to measure the clinical and economic impact of advanced practitioners. The profession must also consider how global harmonization of the definitions of advanced and specialty practice and of credentialing processes could unite and strengthen the international impact of the workforce.

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

THE "PRO" SIDE

The pharmacokinetic-pharmacodynamic parameter best correlated with efficacy of vancomycin in the treatment of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) is the 24-h ratio of area under the curve (AUC) to minimum inhibitory concentration (MIC).[1,2] Given the need for multiple measurements of vancomycin level and complex calculations, the trough level has historically been used as a surrogate marker. In the 2009 guidelines for therapeutic monitoring of vancomycin,[3] troughs of 15–20 µg/mL were recommended, on the basis that these levels should correlate with an AUC/MIC of at least 400 mg*h/L, the true efficacy target. Since the implementation of these recommendations, reports of increased toxic effects have raised concerns about overly aggressive dosing, and clinicians have attempted to identify strategies to better balance targeted clinical efficacy with the risk of toxic effects.

There is known interpatient variability in the correlation between measured trough, which is a single point estimate, and target AUC/MIC.[4-6] Pai and others[5] detailed the mathematical relation between trough and AUC and demonstrated, through Monte Carlo simulations, that only 50% of interindividual variability in exposure is explained by trough values. Pragmatically, Hale and others[6] evaluated vancomycin levels in 100 patients in an attempt to correlate trough concentrations with AUC/MIC of at least 400. They found that troughs less than 10 µg/mL were unlikely to achieve an AUC of at least 400 (p = 0.045); however, there was no difference between troughs of 10–14.9 µg/mL and 15–20 µg/mL (p = 0.817). Therefore, without the corresponding AUC, a trough value alone is minimally useful.

Data regarding the vancomycin trough level as a surrogate marker for AUC/MIC in the context of MRSA bacteremia also highlight that troughs of 15–20 µg/mL are likely to attain the pharmacokinetic-pharmacodynamic target, but may also lead to unnecessary exposure and risk of toxicity.[4,7,8] In their meta-analysis, van Hal and others[7] reviewed 15 studies and found that vancomycin trough levels of 15 µg/mL or above were associated with increased odds of nephrotoxicity relative to trough levels below 15 µg/mL (odds ratio [OR] 2.67, 95% confidence interval [CI] 1.95–3.65), a difference that persisted after adjustment for clinically relevant covariates. Bosso and others[9] came to a similar conclusion when evaluating vancomycin levels in 291 patients across 7 sites. Fifty-five patients met the definition for nephrotoxicity, of whom 76.4% had troughs above 15 µg/mL. In a multivariable analysis, relative to lower trough values, troughs above 15 µg/mL were independently associated with increased risk of nephrotoxicity. These findings are supported by the quasi-experimental study of Finch and others,[10] who examined the impact of changing from trough-based to AUC/MIC-based monitoring. In a study of more than 1000 patients, AUC/MIC-based monitoring was independently associated with lower odds of nephrotoxicity relative to trough-based monitoring (OR 0.53, 95% CI 0.34–0.8).

Data correlating attainment of the target vancomycin trough with improved clinical outcomes are lacking.[11] Jung and others[12] evaluated vancomycin treatment failure in patients with MRSA bacteremia and found no difference in the proportion of treatment failures between those who did and those who did not achieve troughs of 15–20 µg/mL. They did determine that AUC/MIC below 430 was associated with more treatment failure than AUC/MIC above 430 (50% versus 25%, p = 0.039). Kullar and others[11] found a similar result. Among 320 patients, they reported a 52.5% failure rate and found that patients with AUC/MIC below 421 had an increased risk of failure relative to those with AUC/MIC above 421 (61.2% versus 48.6%, p = 0.038). Brown and others[13] found a significant 4-fold increased risk of death with AUC/MIC below 211 (with MIC determined by Etest) relative to AUC/MIC above 211 in patients with MRSA bacteremia and infective endocarditis (63% versus 19%, p = 0.02). Admittedly, most of the literature supporting the use of AUC as a marker of clinical outcomes is based on AUC approximations; nonetheless, these studies still provide more evidence than is available for trough-based monitoring. As outlined above, data supporting either measure to improve clinical outcomes are lacking; however, AUC/MIC-based monitoring to limit toxic effects is more robust than trough-based monitoring. This conclusion is supported by a recent, prospective evaluation of vancomycin AUC/MIC exposures in 265 patients with MRSA bacteremia. Lodise and others[14] were not able to identify an AUC/MIC threshold associated with treatment success but did find that patients with AUC/MIC less than or equal to 515 experienced the best global outcomes, including a limited risk of nephrotoxicity.

As mentioned, vancomycin troughs of 15–20 µg/mL have been recommended as a surrogate marker because of challenges in estimating AUC in clinical practice.[3] The consensus guidelines for therapeutic monitoring of vancomycin have recently been updated to recommend target attainment based on AUC/MIC, stating that use of 2-level AUC calculators or Bayesian software programs now makes quick and reliable calculations feasible.[15] There remains considerable hesitation among clinical pharmacists, however, regarding the practical application of AUC/MIC-based monitoring.[16-18] As reported by those surveyed, common concerns have included unclear benefit of and lack of familiarity with AUC/MIC-based monitoring, training requirements, and resource allocation in terms of pharmacist time and laboratory costs. The paradigm of trough-based monitoring has been so long engrained in clinical practice that the need for extensive education to address the lack of familiarity with AUC/MIC-based monitoring is a valid concern.

To assist others, several clinicians have published their experiences with implementing AUC/MIC-based monitoring.[19-21] These publications highlight the need for extensive education of not only clinical pharmacists, but also front-line nurses, phlebotomists, and ordering providers. This culture change does not happen overnight, but successful implementation of this strategy has proven feasible across numerous and varied practice sites. Although resource allocation related to the number of levels measured per patient is a justifiable concern, recent publications have not supported this.[18,19,22] In a prospective trial investigating a transition from trough-based to AUC/MIC-based monitoring using Bayesian software, Neely and others[23] reported fewer blood samples per patient, shorter duration of therapy, and decreased nephrotoxicity. Numerous programs are now available that utilize richly sampled patient populations and Bayesian-based mathematical modelling to assist in optimizing AUC/MIC without the need to measure vancomycin level numerous times for each patient.[24] Additionally, if the cost of these programs is a concern, 2-level AUC-based calculators, either developed separately or integrated with the electronic medical record, have been commonly used to implement AUC/MIC-based monitoring.[19-21] It is also important to note that among those who have changed to AUC/MIC-based monitoring, the perception of clinical relevance shifts from "unknown" to "of clinical importance", evidence that a paradigm shift is in fact possible.[18,21]

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THE "CON" SIDE

New practices in infectious disease pharmacotherapy are often promoted because they should work, according to our understanding of pathophysiology, microbiology, and pharmacokinetics and pharmacodynamics. However, theoretical advantages frequently fail to produce tangible benefit and occasionally result in harm.[1] Recent examples of failures in the translation from theory to practice include inhaled antibiotics for ventilator-associated pneumonia,[2] combination therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia[3,4] and carbapenem-resistant *Acinetobacter baumannii* infections,[5] and—of particular relevance to the topic of this Point Counterpoint debate—the use of vancomycin troughs of 15 to 20 mg/L to guide treatment for invasive MRSA infections.[6,7] When the first iteration of the vancomycin monitoring guideline was published in 2009,[6] concerns over the emergence of *S. aureus* strains with reduced vancomycin susceptibility led some researchers and clinicians to advocate for an aggressive dosing approach in the absence of high-quality data.[8,9] Since then, evidence has suggested that trough levels of at least 15 mg/L may not be necessary to achieve the guideline target for area under the curve (AUC) of at least 400.[10] Furthermore, the described "creep" in vancomycin minimum inhibitory concentration (MIC) may be an artifact of the testing method, and changes in pathogen virulence and/or lack of source control may often be responsible for antibiotic failure.[11-15] In addition, the clinical benefit of maintaining trough levels between 15 and 20 mg/L has not been well documented, and available data indicate that levels within this range are associated with an increase in nephrotoxicity.[7,16]

The updated vancomycin guideline, published earlier this year, now recommends AUC/MIC monitoring for serious MRSA infections, with abandonment of trough-based monitoring.[17] This recommendation creates a significant shift in how clinicians mange vancomycin therapy and may have substantial monetary and opportunity costs. These costs are justified only if AUC-based monitoring improves clinical or safety outcomes. Below we outline our view that the recommendation for AUC-based monitoring is drawn from weak evidence, which is not sufficient to justify widespread adoption.

The threshold AUC/MIC value of 400 originates from a single-centre, retrospective study of *S. aureus* pneumonia from the early 2000s.[18,19] In that study, an AUC/MIC value greater than or equal to 350, as determined by classification and regression tree analysis (CART) in 50 clinically evaluable patients, was associated with a greater likelihood of clinical success, whereas an AUC/MIC value greater than or equal to 400 (n = 34 patients) was associated with bacterial eradication.[18,19] Several points pertaining to this study deserve emphasis: first, the estimated AUC was calculated on the basis of *all* anti-staphylococcal antibiotics administered during the course of therapy, including combination therapy with ß-lactams and aminoglycosides, for which AUC/MIC is not the relevant pharmacokinetic-pharmacodynamic index; second, the majority (63%) of *S. aureus* isolates were methicillin-susceptible; and finally, the outcome of bacterial eradication from respiratory samples has uncertain clinical value.

Many studies have since examined the relationship between vancomycin AUC/MIC and clinical outcomes in patients with MRSA infections, coming to divergent conclusions and identifying a wide range of thresholds.[20-44] Most have been small (fewer than 100 participants),[23,25,28,30,32,33,35,36,38-40] retrospective,[23-25,27-30,32,33,35,36,38,40-42] single-centre[23,24,27-30,32,33,35,36,38,40,42] studies in which vancomycin dosing was managed by assessment of trough levels.[23,24,27,29,32,34-36,39-43] Study registration, planned analyses, and power calculations were rarely discussed in the published reports. Vancomycin MIC was determined by a variety of testing methods, and many of the studies used formulas to estimate AUC that were based on daily vancomycin dose, population pharmacokinetics, and estimated renal function.[25,27,32,39,42] The guideline authors acknowledged technical issues with determination of vancomycin MIC and suggested the assumption that MIC = 1 mg/L.[17] However, using this assumption for dosing decisions in individual patients is problematic because most studies have not assumed MIC = 1 mg/L. High MIC on its own may be predictive of response, and when used as the denominator, a higher value of MIC drives down the AUC/MIC value, creating a spurious correlation.[45] In addition, in many studies CART was used as an exploratory method to identify cut points for dichotomizing AUC/MIC data without validation in an independent external data set.[23-25,27,28,33,34,38,40] Threshold values

identified by CART have ranged from as low as 211[22] to as high as 667,[28] with some studies identifying multiple thresholds.[21,24,27,29,30] In the only study to date that attempted to validate alternative CART-derived AUC/MIC thresholds (day-2 AUC/MIC ≥ 650 and ≥ 320, with MIC determined by broth microdilution and Etest, respectively) in a multicentre, prospective study of an external population, there was no significant difference in mortality or persistent bacteremia using these vancomycin exposure thresholds.[31] Additionally, that study did not identify alternative thresholds or confirm AUC/MIC of at least 400 as predictive of clinical failure.[31]

Among studies assessing the relationship between clinical outcomes and a prespecified AUC/MIC threshold of 400,[11,32,35,36,39] only one, which involved 51 pediatric patients with *S. aureus* bacteremia, found a statistically significant relationship between AUC/MIC of at least 400 and clinical response[32]; however, no significant association was found between AUC/MIC of at least 400 and mortality or microbiological response. Interestingly, one study found no significant reduction in 30-day mortality among patients with *S. aureus* bacteremia who achieved AUC/MIC of at least 400, but found that an alternative CART-derived threshold of 373 was statistically significant.[44] In another study, patients who experienced clinical failure paradoxically had a significantly higher mean vancomycin AUC than those who experienced clinical success.[37] Many other studies also found no statistically significant relationship between AUC (or AUC/MIC) and outcomes, and therefore the authors did not go on to perform CART (or other) analyses.[35,36,38-43,46] None of these studies reported a formal power calculation, so type II errors cannot be excluded.[11,32,35,36,39] Surprisingly, many studies with negative or nonsignificant results[35,38-43,46] were not mentioned in the guideline update, even though the guideline methods suggested that all relevant literature published in English had been reviewed.[17]

AUC-based vancomycin monitoring may still be valuable if it is a safer alternative than trough-based monitoring. A large body of observational literature collectively suggests that the incidence of nephrotoxicity increases as a function of vancomycin exposure, whether measured by trough level or AUC.[11,31,37,46-57] A wide range of threshold AUC values have been identified (563–1300 mg*h/L),[33,47,54,56,57] and the observational data are conflicting with regard to which pharmacokinetic parameter—trough level or AUC—is most closely correlated with nephrotoxicity.[47,56,57] In some studies, which used Monte Carlo simulation or population pharmacokinetic data to estimate AUC, trough levels have been only moderately correlated with AUC.[10,52] However, recent clinical studies using human data (rather than simulation) have found remarkably high correlation between trough level and AUC (R^2 = 0.88–0.95).[47,49,50,53,58,59] Such high correlation makes distinguishing a "better" measure of exposure a fool's errand, since one predictor can easily and reasonably accurately be approximated by the other.

Two recent observational studies reported lower rates of nephrotoxicity with the implementation of AUC-based monitoring relative to previously used trough-based monitoring.[48,51] Importantly however, all[48] or many[51] patients in the trough-based monitoring arms of these studies received vancomycin regimens targeting trough levels of 15 to 20 mg/L, an approach to vancomycin therapy that is known to be harmful.[7,16] Average doses and trough levels were significantly lower in the AUC-based groups, which reaffirms that lower vancomycin exposure confers a decreased risk of nephrotoxicity, regardless of the monitoring method. An important knowledge gap is the issue of whether AUC-based monitoring is safer than trough-based monitoring that targets pre–guideline era troughs between 5 and 15 mg/L. We hypothesize that there would be little observable difference.

In summary, the collective evidence on vancomycin AUC-based therapeutic drug monitoring for MRSA infections is primarily hypothesis-generating and inconsistent. Although AUC-based monitoring may have appeal because of its perceived sophistication, it has not met the stated criteria of improving clinical outcomes or safety. In fact, the multiple blood samples required for AUC-based monitoring will affect patient comfort and convenience and may cause harm. Pharmacists and other clinicians should advocate for interventions that are valuable to patients and the health care system, rather than assuming that newer, more complex, more expensive, and more time-consuming strategies will lead to better outcomes.

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S'adapter à une pandémie

par Tania Mysak

C'était le 11 mars. Pressés par une échéance se rapprochant à grands pas dans un contexte en pleine mutation, les membres de la direction de l'organisation se sont réunis dans l'urgence pour prendre des décisions importantes sur la base d'informations incomplètes. L'Organisation mondiale de la Santé venait de déclarer que la COVID-19 engendrerait une pandémie mondiale. D'une part, ce n'était qu'une confirmation de ce que l'on savait déjà : un nouveau virus frappant plusieurs continents. D'autre part, cette pandémie a tout modifié et mis en branle des changements qui allaient avoir des conséquences sur notre environnement de travail et notre vie personnelle qu'on ne saisissait pas pleinement à ce moment-là.

La réunion en question portait sur le séminaire de la Société canadienne des pharmaciens d'hôpitaux (SCPH) à Banff. Nous étions rassemblés autour d'un intervenant dans un petit bureau (avant que la distanciation physique ne devienne la norme) pour nous entretenir avec nos collègues et examiner les options qui s'offraient à nous. La conférence devait commencer quelques jours plus tard et Jody Ciufo, directrice générale de la SCPH, qui se réjouissait de participer à son premier séminaire à Banff, avait déjà fait le déplacement. Mais des nuages menaçants pointaient à l'horizon. Le comité de planification filtrait depuis plus d'une semaine les appels d'intervenants, de commanditaires et de participants soucieux. Étant donné ce que nous savions déjà à ce moment-là, pouvions-nous maintenir la conférence? Pouvions-nous assumer les coûts d'une l'annulation? Pouvions-nous courir le risque de ternir la réputation si une épidémie se déclarait parmi les travailleurs de la santé? Finalement, nous avons tiré un trait sur une belle occasion de rencontre entre les membres.

Pourquoi est-ce que je vous raconte cette histoire? Elle illustre simplement avec quelle vitesse la SCPH a dû faire volte-face pour s'adapter à un changement rapide de l'environnement. À l'instar de notre vie et de notre lieu de travail qui ont été bouleversés pour donner lieu à une « nouvelle normalité », la vie à la SCPH a également été mise sens dessus dessous. Le travail et les plans du printemps, de l'été et probablement de l'automne ont été réorientés et leurs priorités redéfinies. Les conférences ont été annulées dans un climat d'incertitude quant à un retour à la normale. Nous avons recentré nos formations pour les orienter sur des webinaires portant sur la COVID-19, qui ont tous été accueillis avec enthousiasme. Nous nous sommes réunis et réajustés pour être sûrs de pouvoir être au bon endroit pour plaider en faveur des médicaments essentiels et prévenir des pénuries dévastatrices. Nos Réseaux de spécialité en pharmacie et notre site Web consacré à la COVID-19 sont devenus des centres animés d'échanges et d'acquisition des connaissances. Nous avons favorisé les réunions et les rencontres virtuelles. Bien qu'il reste encore beaucoup de défis à relever, de nombreux changements ont été positifs et nous permettent d'explorer de nouvelles manières de répondre aux besoins des membres et de faire avancer nos pratiques. Soutenir les membres de la SCPH et leurs patients tout au long de la pandémie de COVID-19 est un travail à la fois considérable et gratifiant.

Quand vous lirez ces quelques lignes, nous devrions avoir dépassé le premier pic de ce qui devrait être une série de vagues qui frappent notre système de soins de santé. Comme cette expérience a permis d'attirer l'attention de la société sur le besoin fondamental d'un système de santé publique solide, j'espère qu'elle a également attiré l'attention de notre communauté de pharmaciens sur le besoin crucial d'une société professionnelle solide. J'espère que vous avez été témoins de la contribution qu'apporte la SCPH à la pratique de la pharmacie et aux relations professionnelles. Finalement, j'espère aussi sincèrement que vous avez fait remarquer cette contribution aux non-membres et que vous les avez encouragés à se joindre à nous pour poursuivre notre mission primordiale.

[Traduction par l'éditeur]

Tania Mysak, B.S.P., Pharm. D., est présidente et agente de liaison pour la vision de la Société canadienne des pharmaciens d'hôpitaux.

Pivoting for a Pandemic

Tania Mysak

It was March 11. Organizational leadership had quickly gathered to make a critical decision with incomplete information, a deadline fast approaching, and in the context of shifting sands. The World Health Organization had just declared COVID-19 to be a global pandemic. On one hand, it was merely an acknowledgement of what was already known—a novel virus impacting multiple continents. On the other hand, it changed everything, setting in motion changes that would affect our work environments and personal lives in ways we did not fully comprehend.

The meeting in question was about the Canadian Society of Hospital Pharmacists' (CSHP's) Banff Seminar. We were huddled around a speaker in a small office (before physical distancing became the norm), conferring with colleagues and reviewing the options. The conference was scheduled to start within days, and Jody Ciufo, CSHP's Chief Executive Officer, had travelled to attend her first Banff Seminar in an atmosphere of eager anticipation. But storm clouds were gathering. The planning committee had been fielding calls for over a week from concerned speakers, sponsors, and participants. Given what we knew even at that point, could we continue with the conference? Could we afford the costs of cancellation? Could we afford the reputational risk of an outbreak among healthcare workers if we proceeded? In the end, we pulled the plug on a beloved connection point for members.

Why am I sharing this story with you? It's a simple illustration of how quickly CSHP had to pivot and adapt to a rapidly changing environment. Just as our personal lives and workplaces have been uprooted with change and chaos and a "new normal", so has CSHP life. The work and plans of the spring, summer, and possibly even the fall, have been refocused and reprioritized. Conferences were cancelled amid uncertainty as to when things would return to "normal". We shifted the focus of education to COVID-19 related webinars—all enthusiastically received. We regrouped and recalibrated to ensure we were at the right tables to advocate for critical drugs and prevent devastating shortages. Our Pharmacy Specialty Networks and COVID-19 website have become bustling hubs of knowledge gathering and sharing. We embraced virtual meetings and connections. While there are still challenges ahead, many changes have been positive and allow us to explore new ways to meet member needs and advance our practices. Supporting CSHP members and their patients through COVID-19 is the job—overwhelming and gratifying all at the same time.

By the time you read this, we should be past the first peak of what is anticipated to be a series of waves to hit our healthcare system. Just as the experience has awakened society to the critical need for a strong public health system, I hope that it has also awakened our pharmacy community to the critical need for a strong professional society. I hope you have seen CSHP demonstrate the value we bring to pharmacy practice and to professional connections. Finally, I really hope you have shared that value with non-members and encouraged them to join and allow us to continue our critical work.

Tania Mysak, BSP, PharmD, is President and Vision Liaison for the Canadian Society of Hospital Pharmacists.

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