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Don't Stress about Ulcer Prophylaxis

Robert MacLaren

A common medical doctrine is that critically ill patients require stress ulcer prophylaxis (SUP) to prevent gastrointestinal bleeding (GIB) caused by mucosal ischemia from physiologic stress. Withholding or de-escalating SUP in a patient at risk for GIB may be perceived as medical misconduct or a failure to meet benchmark performance measures. SUP is so ingrained in practice that many intensive care units (ICUs) have admission order sets that specify automatic initiation of SUP. Unfortunately, the inadvertent consequence of improvident SUP in the ICU is the spread of this practice to patients without an indication for SUP. The declining rate of GIB and the association between acid suppression and infectious complications have generated skepticism regarding SUP. Two years ago in this journal, Yamashita and Duffett argued in favour of and against SUP in a Point Counterpoint debate.[1,2] My purpose here is to highlight additional considerations, including key findings of recently published studies, to emphasize the ongoing clinical dilemma of SUP.

The 2 most commonly quoted risk factors for stress-related GIB are mechanical ventilation and coagulopathy. These risk factors are derived from an observational study of 2252 ICU patients, in which investigators requested that SUP be withheld unless a patient had head injury, extensive thermal burns, transplant, or a recent peptic ulcer or GIB; ultimately, 674 patients received SUP and 1578 did not.[3] The presence of hypotension trended toward a significant association with GIB. The primary indication in 54.8% of the patients was cardiovascular disease or surgery, for which medical practices have evolved from primarily anticoagulation and surgery to noninvasive interventional radiologic techniques. Few patients had a diagnosis of central nervous system injury, sepsis, head injury, or multiple trauma. Noninvasive ventilation was not routinely used at the time of publication. Therefore, the results of this study must be considered in the context of the population evaluated, the exclusion of patients with potential risk factors, and changes in medical practices since its publication. Fast forward to today and the recent publication of a meta-analysis of 8 studies (116 497 patients), which showed that coagulopathy, shock, and chronic liver disease were associated with clinically important GIB, but mechanical ventilation was not.[4] Those favouring SUP will note that most of the included studies used SUP, so these parameters should be considered risk factors when SUP is administered, whereas opponents of SUP will highlight the lack of consistency across the studies and question whether "established" risk factors are truly known.

While goals of therapy focus on mortality, clinically important GIB, and infectious complications, SUP is commonly prescribed with little concern about the advantages and disadvantages of particular agents. The histamine-2 receptor antagonists (H2RAs) are commonly employed on the basis of a randomized, double-blind study of 1200 mechanically ventilated patients, which showed a lower rate of clinically significant GIB with ranitidine than with sucralfate (1.7% versus 3.8%, $p = 0.02$).[5] However, a recent meta-analysis that included this study found no difference in clinically important GIB between H2RAs and sucralfate, but less pneumonia with sucralfate.[6] Of note, most of the included studies involved administration of H2RAs by infusion and/or dose adjustment to achieve gastric pH values above 3.5–4, both of which may alter the gastrointestinal microbiome to enhance infection risk to a greater extent than conventional, intermittent H2RA administration. The results of a recent meta-analysis suggest lower GIB with proton pump inhibitors (PPIs) than H2RAs[7]; however, the results were driven by 2 studies with methodological flaws. In contrast, pharmacoepidemiologic analyses found lower rates of pneumonia and *Clostridioides difficile* infection with H2RAs, which again suggests that the extent of acid suppression contributes to microbiome disturbances.[8,9] More recently, a randomized, double-blind, placebo-controlled study found lower rates of clinically important GIB with pantoprazole (2.5% versus 4.2%, relative risk 0.58, 95% confidence interval 0.4–0.86).[10] Although infectious complications and the primary outcome of 90-day mortality were similar between groups, a post hoc analysis showed higher mortality rates with pantoprazole in the most severely ill patients (i.e., those most likely to have risk factors for GIB).[11] Taken together, these data confound the choice of which class of agents is preferred for SUP and highlight

the need to define which outcomes are most important. Although GIB is associated with prolonged ICU stay and additional costs, no study has shown a mortality benefit with SUP. The risk of infectious complications and the unexplainable higher rate of mortality in the post hoc analysis of the most recent study[11] generate uncertainty surrounding the routine practice of SUP.

The decline in stress-related GIB over the past few decades may be explained, in part, by more effective SUP strategies or by contemporary medical practices (such as aggressive hemodynamic resuscitation) that limit mucosal ischemia. Early administration of enteral nutrition may offer GIB protection to the extent that the effectiveness of pharmacologic SUP is minimized.[12] At the very least, tolerance to enteral nutrition suggests that gastrointestinal reperfusion has occurred, whether or not risk factors for GIB remain present. The duration of SUP has been shortened substantially, with the most recent study suggesting about 4 days of therapy, which coincides with when GIB is most likely to occur after ICU admission.[10] Unfortunately, real-world practice does not reflect this trend, as 25% of patients unnecessarily continue to receive SUP after hospital discharge. The argument for or against SUP should not focus on the universal adoption or abandonment of the practice but instead on how to rationalize appropriate use to optimize GIB prevention while limiting exposure and minimizing adverse consequences. Rather than discontinuing therapy, the safer practice model is to limit SUP orders to 2–3 days, with longer durations necessitating a new order by the prescriber. In the study of risk factors, the rate of GIB was substantially higher in the cohort that received SUP (16.3% versus 1.5%).[3] Some may argue that this suggests SUP is ineffective, when really it reflects selection bias, with clinicians being more likely to provide SUP to patients perceived to be at higher risk of GIB. Pending studies and new guidelines may resolve some uncertainties but in the meantime it is important to understand the clinical equipoise surrounding SUP and to ensure appropriate SUP therapy, while dispelling the belief that SUP is a rite of passage in the ICU.

References

1. Yamashita S. Should we continue stress ulcer prophyalxis for critically ill patients? The "pro" side. *Can J Hosp Pharm*. 2017;70(4):316-7.
2. Duffett M. Should we continue stress ulcer prophyalxis for critically ill patients? The "con" side. *Can J Hosp Pharm.* 2017;70(4):317-8.
3. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, et al.; Canadian Critical Care Trials Group. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med*. 1994;330(6):377-81.
4. Granholm A, Zeng L, Dionne JC, Perner A, Marker S, Krag M, et al. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med*. 2019;45(10):1347-59.
5. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al.; Canadian Critical Care Trials Group. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med.* 1998;338(12):791-7.
6. Alquraini M, Alshamsi F, Møller MH, Belley-Cote E, Almenawer S, Jaeschke R, et al. Sucralfate versus histamine 2 receptor antagonists for stress ulcer prophylaxis in adult critically ill patients: a meta-analysis and trial sequential analysis of randomized trials. *J Crit Care*. 2017;40:21-30.
7. Alshamsi F, Belley-Cote E, Cook D, Almenawer SA, Alqahtani Z, Perri D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care.* 2016;20(1):Article 120.
8. Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, et al.; SUP-ICU Trial Group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199-208.
9. Marker S, Perner A, Wetterslev J, Krag M, Lange T, Wise MP, et al.; SUP-ICU Investigators. Pantoprazole prophylaxis in ICU patients with high severity of disease: a post hoc analysis of the placebo-controlled SUP-ICU trial. *Intensive Care Med*. 2019;45(5):609-18.
10. Lilly CM, Aljawadi M, Badawi O, Onukwugha E, Tom SE, Magder LS, et al. Comparative effectiveness of proton pump inhibitors vs histamine type 2 receptor blockers for preventing clinically important gastrointestinal bleeding during intensive care: a population-based study. *Chest*. 2018;154(3):557-66.
11. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med*. 2014;174(4): 564-74.
12. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. *Crit Care.* 2018;22(1):Article 20.

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Prévention des ulcères : pas de stress!

par Robert MacLaren

Une théorie médicale répandue veut que les patients gravement malades nécessitent une prophylaxie de l'ulcère de stress (PUS) pour prévenir le saignement gastro-intestinal (SGI) engendré par une ischémie de la muqueuse à la suite d'un stress physiologique. Refuser la PUS à un patient présentant un risque de SGI ou la désamorcer peut être perçu comme une inconduite médicale ou un manquement au respect des mesures standard de rendement. La PUS est tellement ancrée dans la pratique que de nombreux services de soins intensifs (SSI) disposent de modèles d'ordonnances normalisés au moment de l'admission, qui stipulent d'entreprendre automatiquement la PUS. Malheureusement, la conséquence involontaire de son déclenchement irréfléchi dans les SSI résulte en la propagation de cette pratique aux patients ne présentant pas d'indication de PUS. Le taux en baisse du SGI ainsi que l'association entre la suppression de l'acide et les complications infectieuses sont sources de scepticisme à l'égard de la PUS. Il y a deux ans, Yamashita et Duffett plaidaient dans ce journal en faveur de la PUS et contre elle à l'occasion d'un débat où s'affrontaient le pour et le contre[1,2]. Mon objectif vise ici à mettre en évidence d'autres considérations, y compris certains résultats clés d'études récemment publiées, pour attirer l'attention sur le dilemme clinique persistant relatif à la PUS.

Les deux facteurs de risque de SGI lié au stress les plus communément cités sont la ventilation mécanique et la coagulopathie. Ces facteurs de risque sont mentionnés dans une étude observationnelle menée auprès de 2252 patients des SSI. Dans cette étude, les chercheurs ont demandé la suspension de la PUS, à moins que le patient soit atteint d'un traumatisme crânien, qu'il ait subi des brûlures thermiques importantes ou une greffe, qu'il ait souffert récemment d'un ulcère peptique ou d'un SGI; finalement, 674 patients ont reçu une PUS et 1578 n'en ont pas reçu[3]. La présence d'hypotension tendait à être significativement associée au SGI. L'indication principale, qui concernait 54,8 % des patients, mentionnait une maladie cardiovasculaire ou une chirurgie, pour lesquelles les pratiques médicales avaient évolué principalement de l'anticoagulation et de la chirurgie aux techniques d'intervention radiologique non invasives. Peu de patients avaient reçu un diagnostic de lésion du système nerveux central, de septicémie, de traumatisme crânien ou de traumatismes multiples. La ventilation non invasive n'était pas systématiquement utilisée au moment de la publication de l'étude. Par conséquent, la lecture des résultats de cette étude doit s'inscrire dans le contexte de la population évaluée, de l'exclusion des patients présentant des facteurs de risque et des changements aux pratiques médicales qui ont eu lieu depuis leur publication. Revenons à aujourd'hui et à la publication récente d'une méta-analyse portant sur huit études (116 497 patients), qui démontre que la coagulopathie, le choc et la maladie hépatique chronique sont associés à un SGI important sur le plan clinique, mais que la ventilation mécanique ne l'est pas[4]. Les personnes en faveur de la PUS noteront que la plupart des études incluses dans cette méta-analyse y ont eu recours; il faut donc considérer ces paramètres comme des facteurs de risque lors de l'administration de cette prophylaxie. Les adversaires de la PUS souligneront quant à eux le manque d'uniformité des études et ils voudront également savoir si les facteurs de risque « établis » sont véritablement connus.

Alors que les objectifs de la thérapie se concentrent sur la mortalité, sur le SGI cliniquement important et sur les complications infectieuses, on prescrit communément la PUS sans se préoccuper vraiment des avantages et des inconvénients de chaque agent. L'usage courant des antagonistes du récepteur H2 de l'histamine (H2RA) repose simplement sur une étude randomisée en double aveugle, qui a été menée auprès de 1200 patients ventilés mécaniquement; celle-ci a révélé un taux moins élevé de SGI cliniquement significatifs sous l'effet de la ranitidine plutôt que de la sucralfate (1,7 % contre 3,8 %, $p = 0,02$)[5]. Pourtant, une méta-analyse récente incluant cette étude décisive n'a trouvé aucune différence de SGI cliniquement importante en présence des H2RA et de la sucralfate, mais il y avait moins de pneumonie en présence de la sucralfate[6]. Notons que la plupart des études incluses impliquaient l'administration des H2RA par infusion ou adaptation posologique pour obtenir des valeurs de pH gastriques supérieures à 3,5-4. Ces deux aspects de l'administration du médicament peuvent modifier le microbiome gastro-intestinal, ce qui augmente le risque d'infection dans une plus large mesure que l'administration conventionnelle et intermittente de H2RA. Les résultats d'une récente méta-analyse n'indiquent une SGI inférieure avec des inhibiteurs de la pompe à protons (PPI) qu'avec des H2RA[7]; cependant, les résultats étaient influencés par deux études

présentant des lacunes méthodologiques. En revanche, les analyses pharmacoépidémiologiques ont révélé des taux de pneumonie et d'infection de *Clostridioides difficile* moins importants en présence des H2RA; cela permet à nouveau de penser que le degré d'importance de la suppression d'acide contribue aux perturbations du microbiome[8,9]. Plus récemment, une étude randomisée en double aveugle et contrôlée par placebo a mis en évidence des taux plus faibles de SGI cliniquement importants en présence de pantoprazole (2,5 % contre 4,2 %, risque relatif 0,58; 95 % intervalle de confiance 0,4–0,86)[10]. Malgré la similitude des complications infectieuses et le résultat principal qui portait sur la mortalité 90 jours après le traitement, tous groupes confondus, une analyse *post hoc* a démontré des taux de mortalité plus élevés sous l'effet du pantoprazole parmi les patients les plus gravement malades (c.-à-d. ceux qui sont le plus exposés aux facteurs de risque de SGI)[11]. L'ensemble de ces données compliquent le choix de la classe d'agents à privilégier pour entreprendre une PUS, ce qui met en évidence le besoin de définir quels résultats sont les plus importants. Malgré que le SGI soit associé à un séjour prolongé en SSI et à des coûts supplémentaires, aucune étude n'a démontré d'avantage sur la mortalité après une PUS. Le risque de complications infectieuses et les taux de mortalité plus élevés que l'analyse *post hoc* de l'étude la plus récente ne peut pas expliquer[11] créent de l'incertitude entourant la pratique courante de la PUS.

Le déclin du SGI lié au stress au cours des dernières décennies s'explique en partie par l'efficacité supérieure des stratégies de PUS ou par des pratiques médicales contemporaines (comme la réanimation hémodynamique énergique) qui limitent l'ischémie de la muqueuse. L'administration précoce de nutrition entérale peut protéger contre le SGI dans la mesure où l'efficacité de la PUS pharmacologique diminue[12]. En dernier lieu, la tolérance à la nutrition entérale signifie que la reperfusion gastro-intestinale s'est déroulée, que les facteurs de risque de SGI demeurent présents ou non. La durée de la PUS a grandement diminué, puisque l'étude la plus récente propose environ quatre jours de thérapie, ce qui coïncide avec le moment où le SGI risque le plus de se produire après l'admission dans les SSI[10]. Malheureusement, la pratique actuelle ne reflète pas cette tendance, puisque 25 % des patients continuent de recevoir inutilement une PUS après leur congé de l'hôpital. L'argument pour ou contre la PUS ne devrait pas se focaliser sur l'adoption ou l'abandon universel de la pratique, mais plutôt sur la manière de rationaliser sa bonne utilisation pour optimiser la prévention du SGI, tout en limitant l'exposition aux médicaments et en réduisant les conséquences négatives. Plutôt que de cesser la thérapie, les investigateurs proposent un modèle de pratique plus sûr, qui consiste à limiter les ordonnances de la PUS à deux ou trois jours, alors que la prolongation de la durée nécessiterait une nouvelle ordonnance du prescripteur. L'étude des facteurs de risque a révélé que le taux de SGI était considérablement plus élevé dans la cohorte ayant reçu une PUS (16,3 % contre 1,5 %)[3]. Certains pourraient prétendre que ce résultat est un signe d'inefficacité de la PUS, alors qu'il reflète plutôt un biais de sélection : les cliniciens étant en effet plus enclins à administrer une PUS aux patients perçus comme présentant un risque plus élevé de SGI. Les études en cours et les nouvelles lignes directrices pourraient faire la lumière sur certaines incertitudes, mais entretemps, il est important de comprendre l'équilibre clinique entourant la PUS et d'assurer une thérapie appropriée en la matière, tout en dissipant la croyance selon laquelle elle serait un rite de passage obligatoire dans les SSI.

[Traduction par l'éditeur]

Références

1. Yamashita S. Should we continue stress ulcer prophyalxis for critically ill patients? The "pro" side. *Can J Hosp Pharm.* 2017;70(4):316-7.
2. Duffett M. Should we continue stress ulcer prophyalxis for critically ill patients? The "con" side. *Can J Hosp Pharm*. 2017;70(4):317-8.
3. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, et al.; Canadian Critical Care Trials Group. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med*. 1994;330(6):377-81.
4. Granholm A, Zeng L, Dionne JC, Perner A, Marker S, Krag M, et al. Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis. *Intensive Care Med*. 2019;45(10):1347-59.
5. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al.; Canadian Critical Care Trials Group. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med*. 1998;338(12):791-7.
6. Alquraini M, Alshamsi F, Møller MH, Belley-Cote E, Almenawer S, Jaeschke R, et al. Sucralfate versus histamine 2 receptor antagonists for stress ulcer prophylaxis in adult critically ill patients: a meta-analysis and trial sequential analysis of randomized trials. *J Crit Care.* 2017;40:21-30.
7. Alshamsi F, Belley-Cote E, Cook D, Almenawer SA, Alqahtani Z, Perri D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care*. 2016;20(1):Article 120.
8. Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, et al.; SUP-ICU Trial Group. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199-208.
9. Marker S, Perner A, Wetterslev J, Krag M, Lange T, Wise MP, et al.; SUP-ICU Investigators. Pantoprazole prophylaxis in ICU patients with high severity of disease: a post hoc analysis of the placebo-controlled SUP-ICU trial. *Intensive Care Med.* 2019;45(5):609-18.
10. Lilly CM, Aljawadi M, Badawi O, Onukwugha E, Tom SE, Magder LS, et al. Comparative effectiveness of proton pump inhibitors vs histamine type 2 receptor blockers for preventing clinically important gastrointestinal bleeding during intensive care: a population-based study. *Chest.* 2018; 154(3):557-66.
11. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med.* 2014;174(4): 564-74.
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Evaluation of a Novel Audit Tool for Medication Reconciliation at Hospital Discharge

Anne Holbrook, Heather Bannerman, Amna Ahmed, Michael Georgy, J Tiger Liu, Sue Troyan, and Alice Watt

ABSTRACT

Background: Discharge medication reconciliation (MedRec) is designed to reduce medication errors and inform patients and key postdischarge providers, but it has been difficult to implement routinely in Canadian hospitals.

Objectives: To evaluate and optimize a new discharge MedRec quality audit tool and to use it at 3 urban teaching hospitals.

Methods: The discharge MedRec quality audit tool, developed by the Canadian Patient Safety Institute and the Institute for Safe Medication Practices Canada, was assessed and modified to improve comprehensiveness, clarity, and quality. The modified tool was then used to evaluate the quality of the discharge MedRec process for adult patients discharged to home from the general internal medicine service at 3 academic hospitals. Postdischarge telephone interviews were conducted with consenting patients, their community pharmacists, and their family doctors.

Results: The audit tool required modification to include aspects of admission MedRec, high-risk medication discrepancies, and direct communication of discharge MedRec to key follow-up providers. Thirty-five patients (mean age 67.7 years, standard deviation [SD] 18.0 years; 17 [49%] women), with a mean of 8.8 (SD 4.5) prescribed medications at discharge, participated in the discharge MedRec evaluation. Documentation of any discharge MedRec was found for only 1 patient (3%), and no discharge MedRec was carried out by pharmacists. Postdischarge follow-up interviews elicited major gaps in communication with community pharmacists and with family physicians, which could lead to serious medication errors.

Conclusions: The modified audit tool was useful for identifying gaps in the quality of discharge MedRec.

Keywords: medication error, hospital discharge, medication reconciliation, discharge prescription, quality improvement, accreditation

RÉSUMÉ

Contexte : Le bilan comparatif des médicaments (BCM) au moment du congé est conçu pour réduire les erreurs médicamenteuses et informer les patients ainsi que les principaux prestataires de soins de santé après le congé, mais sa mise en œuvre systématique dans les hôpitaux canadiens s'est heurtée à de grandes difficultés.

Objectifs : Évaluer et optimiser un nouvel outil d'évaluation de la qualité du BCM au moment du congé et l'utiliser dans trois hôpitaux universitaires urbains.

Méthodes : Cet outil développé par l'Institut canadien pour la sécurité des patients (ICSP) et l'Institut pour la sécurité des médicaments aux patients du Canada (ISMP) a fait l'objet d'une évaluation et d'une modification visant à améliorer son exhaustivité, sa clarté et sa qualité. L'outil modifié a ensuite servi à évaluer la qualité du processus du BCM pour des patients adultes ayant obtenu leur congé après un séjour dans un service général de médecine interne dans trois hôpitaux universitaires. Des entretiens téléphoniques après le congé ont été menés avec les patients consentants, leur pharmacien communautaire et leur médecin de famille.

Résultats : L'outil d'évaluation a dû être modifié pour inclure le BCM au moment de l'admission, des écarts de médication à haut risque et une communication directe du BCM aux prestataires de soins de santé principaux chargés du suivi après le congé. Trente-cinq patients (âge moyen : 67,7 ans; écart type [ET] 18 ans; 17 [49 %] femmes), chacun ayant reçu en moyenne 8,8 (ET 4,5) médicaments prescrits, ont participé à l'évaluation du BCM au congé de l'hôpital. Au moment du congé, on n'a trouvé de renseignements relatifs au BCM que pour un seul patient (3 %) et aucun BCM n'avait été préparé par les pharmaciens. Le suivi après le congé a généré des écarts de communication importants entre les pharmaciens communautaires et les médecins de famille, ce qui pourrait entraîner des erreurs médicamenteuses importantes.

Conclusions : L'outil d'évaluation modifié a été utile pour déterminer les écarts relatifs à la qualité du BCM au moment du congé.

Mots-clés : erreur de médication, congé de l'hôpital, bilan comparatif des médicaments, prescription au moment du congé, amélioration de la qualité, accréditation

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INTRODUCTION

Medication error and therapeutic misadventure are thought to be leading causes of preventable patient harm resulting in serious outcomes, including hospital admission and premature death.[1,2] A prospective single-arm cohort study in a Vancouver teaching hospital suggested that 12.0% of emergency department visits were drug-related, of which 68.0% were considered preventable and 36.9% led to hospital admission with a more prolonged length of stay than non–drug-related admissions.[3] The landmark Canadian Adverse Events Study, published in 2004, found that errors with drugs and fluids were the most common cause of harm for inpatients on internal medicine services country-wide, at 42.6% of total errors.[4] The overall fatality rate of 20.8% combined with estimated preventability of 36.9% suggest that there may be up to 5608 preventable deaths in Canadian hospitals each year due to medication error.[4] The US Institute of Medicine has estimated that medication errors cause more deaths every year in the United States than motor vehicle crashes or breast cancer.[5] A recent report from the United Kingdom suggests that medication errors plus drugs of abuse account for more than a third of avoidable deaths.[6]

Transitions in and out of hospital create opportunities for medication errors.[7-9] Unintended medication discrepancies—that is, unaccounted variations from the patient's last known medication list—are an imperfect but commonly used surrogate for medication errors.[10] Errors in medication histories at admission are common, occurring in up to 67% of cases, and many are potentially clinically important.[8,11-14] Fragmented communication in these transitions has been previously documented as a major problem.[15,16]

Although medication discrepancies at admission are important, discrepancies at discharge may result in a higher number of potential adverse drug events.[17] A study of 204 medical-surgical inpatients showed that more than half experienced medication discrepancies during their hospital stay, with 59% of the discrepancies likely to have caused patient harm if the error continued after discharge.[18] In a study completed at a Canadian tertiary care hospital, 70.7% of internal medicine patients had at least 1 actual or potential unintentional medication discrepancy at hospital discharge, with 29.5% of the errors judged to be potentially clinically significant.[19]

Despite potential benefit, there continues to be no evidence that patient outcomes are improved by medication reconciliation (MedRec) itself.[20-23] However, discharge MedRec is mandated by national hospital accreditation bodies in Canada and the United States[24,25] and has been recommended by the National Institute of Health and Care Excellence in the United Kingdom.[26] A recent randomized trial suggested that extensive discharge MedRec, with direct communication to community providers plus several motivational interviews with patients, might reduce readmissions at 6 months.[27] To date, there has not been a standardized, validated tool or methodology to carry out discharge MedRec, a possible reason why it has failed to affect clinical outcomes. The Canadian Patient Safety Institute, the Institute for Safe Medication Practices Canada (ISMP Canada), and others recently developed standardized tools for assessing the quality of MedRec both at hospital admission and at discharge.[28,29]

Our objective in this study was to evaluate a new discharge MedRec quality audit tool and to then use it to evaluate the quality of discharge MedRec in 3 academic teaching hospitals.

METHODS

Ethics approval was obtained from the Hamilton Integrated Research Ethics Board (13-841 and 13-842). The research was conducted in accordance with the principles set forth in the Helsinki Declaration.

Study Design and Setting

This retrospective observational pilot study was conducted at the Juravinski Hospital, Hamilton General Hospital, and St Joseph's Healthcare Hamilton between 2015 and 2018.

Participants and Recruitment

Patients were eligible for inclusion in the study if they were 18 years of age or older, English-speaking, hospitalized for at least 24 h, and discharged to home. Exclusion criteria included discharge to a long-term care facility (where medications are administered by nursing staff) and receipt of palliative care. Patients provided written informed consent. If the patient was unable to consent, a caregiver could consent on the patient's behalf.

Eligible patients and their caregivers were approached within 2 days before discharge. Rolling week-long recruitment periods in each hospital took place, with a target sample size of 30 patients across all 3 hospitals, without a requirement for equal numbers per site. The patients' consent forms and an overview of the study were then faxed to their respective family physicians and community pharmacies to inform them of patient enrolment and to request permission to interview them about MedRec communication with the patient.

Data Collection

We carried out an initial pilot test of the discharge MedRec quality audit tool.[30] This audit tool included checklists identifying sources of information, completeness of the discharge prescription, discrepancies, rationale for discrepancies, resolution of discrepancies, and communication of discharge medication information. Notes regarding the quality of the audit tool as well as suggestions for improvement were recorded, and the tool was modified accordingly. The tool was then tested at the 3 study sites.

Hospital charts for eligible patients were reviewed, including admission notes; best possible medication history (BPMH) on admission, if available; Drug Profile Viewer for Ontario Drug

Benefit recipients, if available[31]; discharge prescription; discharge notes regarding medications; and discharge summaries. Each participant's pharmacy was contacted and asked to provide the patient's medication profile for the 6 months before admission. Presence and absence of these files and types of information, as well as medication discrepancies between the individual files, were recorded for data analysis.

A best possible medication discharge plan (BPMDP) was constructed by reviewing the discharge prescription, the medication administration record for the day of discharge, and the BPMH (either as documented in the chart or created by the investigators, if not present in the chart).

Telephone Interviews

Within 7 days after each participant's discharge from hospital, investigators attempted to contact the participant, the participant's community pharmacy, and the participant's family physician for phone interviews.

The participant interview gathered information about satisfaction with the admission and discharge MedRec processes, what the patient did with the discharge prescription, the patient's understanding of the discharge medications, and satisfaction with the community pharmacy's and family physician's awareness of medication changes after discharge.

The interview with the participant's community pharmacist asked whether the pharmacy had received a discharge prescription and whether changes had been made to the patient's medication regimen. If so, the pharmacy was asked whether these changes had been made clear on the discharge prescription.

The interview with the participant's family physician asked whether the patient had already attended a follow-up post-discharge appointment, whether the physician's office had received a copy of the discharge prescription or discharge summary, and whether any changes to preadmission medications were made clear.

Outcomes

The primary outcome was the usability of the discharge MedRec quality audit tool for internal medicine patients. Secondary outcomes included the quality of the discharge process for medications and the postdischarge opinions of patients, community pharmacists, and family physicians regarding the effectiveness of MedRec at discharge.

Analysis

The analysis was descriptive. Information collected through hospital chart review and phone interviews was entered into a Microsoft Excel database (Microsoft Corporation, Redmond, Washington). After training on chart review and data analysis, 2 of the investigators (H.B., A.A.) independently reviewed all information obtained during the data collection phase, and entered data on discrepancies between the BPMH, discharge summary, and discharge prescriptions, while another investigator (A.H.) assessed the clinical importance of the discrepancies identified using the US Institute for Safe Medication Practices' designation for high-alert medications in the ambulatory setting (i.e., medications that are more likely to result in adverse clinical outcomes if administered incorrectly).[32] Disagreements were resolved by repeat review and consensus.

The completeness, readability, and quality of the discharge prescription itself were also rated (e.g., inclusion of legible prescriber signature, printed full name, and College of Physicians and Surgeons of Ontario number).

RESULTS

We recruited 35 patients from the 3 Hamilton teaching hospitals, with a mean age of 67.7 years (standard deviation [SD] 18.0; range 22–97), of whom 17 (49%) were women (Table 1). The mean number of prescribed medications at discharge was 8.8 (SD 4.5).

Table 1. Baseline Characteristics

Characteristic	No. (%) of Participants* (*n* = 35)
Participants by site	
Site 1	16 (46)
Site 2	10 (28)
Site 3	9 (26)
Age (years) (mean ± SD)	67.7 ± 18.0
Sex	
Male	18 (51)
Female	17 (49)
Hospital length of stay (days) (mean ± SD)	6.4 ± 6.0
Interval between discharge and patient interview (days) (mean ± SD)	11.0 ± 6.0
No. of prescription medications at discharge (mean ± SD)	8.8 ± 4.5
Best possible medication history on file	11 (31)
Discharge prescription received at discharge	33 (94)†
Type of physician signing discharge prescription (*n* = 33)	
Resident	19 (58)
Attending physician	13 (39)
No signature	1 (3)
Discharge prescription included printed name of prescriber (*n* = 33)	22 (67)
Discharge prescription included licence number of prescriber (*n* = 33)	22 (67)
Interviews	
With patients or caregivers (median time after discharge: 9 [IQR 6] days)	31 (89)
With patient's community pharmacist (median time after discharge: 9 [IQR 6] days)	35 (100)
With patient's family physician (median time after discharge: 13 [IQR 24] days)	32 (91)‡

IQR = interquartile range, SD = standard deviation.
*Except where indicated otherwise.
†Two patients were advised to resume their home medications at discharge.
‡Three patients had no family physician.

Evaluation and Modification of the Discharge MedRec Quality Audit Tool

The tool was judged to be missing some key items, which were added to create a modified discharge MedRec tool, as shown in Figure 1. We added items regarding admission MedRec (i.e., the BPMH), high-risk medications, and number of discrepancies. The modified discharge MedRec quality audit tool was judged to have good utility and was easy to use for subsequent assessment of the quality of the discharge MedRec process. Audit questions about prescription details (dose, strength, route of administration, frequency, and duration for each medication; documentation of rationale for medication changes; whether changes to medications were reviewed with the patient and/or caregiver; and whether changes to medications were communicated to community health care providers) were thought to have good face validity for assessing the quality of discharge MedRec.

Quality of MedRec

The quality of MedRec was evaluated for all 35 participants (Table 2). Eleven (31%) of the participants had MedRec completed upon admission (as the BPMH). Of these 11, the BPMH clarified additional medications or dosages in 7 (64%) cases. Mention of a formal discharge MedRec was found for only 1 patient. In 17 cases (49%), it was clear that the discharge prescription had been written directly from the medication administration record on the day of discharge, and up to one-third of prescriptions were missing important information, such as legible prescriber identification or medication details. Using our reconstructed BPMH and BPMDP, we noted a large number of medication discrepancies, involving 22 (63%) of the patients. For 9 (41%) of these 22 patients, unexplained discrepancies involved high-alert medications (as identified by the US Institute for Safe Medication Practices), medications that are more likely to result in adverse clinical outcomes if administered incorrectly.[32] The rationale for medication changes was documented somewhere in the chart in 6 (17%) cases, but none of these charts stated whether the changes had been reviewed with the patient or caregiver at any point.

Postdischarge Interviews

Thirty-one (89%) of the 35 participants were interviewed (Table 2). One patient died before the interview date, and 3 of the patients could not be reached by phone, despite a minimum of 7 call attempts. Twelve (39%) of the 31 participants recalled admission MedRec (BPMH), although only 11 had documentation of admission MedRec in their charts. Several patients noted problems with administration of their medications in hospital, mainly changes in administration times or product substitution. Twenty patients (65%) recalled a "discharge MedRec" process, whereas the criteria for a full review of medications and changes

	A	B	C	D	E	F	G	H	I	J
Patient	Admission MedRec Performed (BPMH): Source #1_____ Source #2_____	Patient discharged to:	Discharge MedRec performed by: ----------	BPMH and Admission Medication orders are accounted for on the discharge medication documentation (BPMDP)	Were there any outstanding discrepancies between the 24 hour MAR and the discharge medication documentation (BPMDP)	Each medication on the discharge medication documentation has: drug name, dose ± strength, route, frequency, legible signature	Prescriber has documented rationale for added, changed or discontinued medications on discharge medication documentation	Discharge medication documentation has been provided and reviewed with the patient/caregiver	The discharge medication documentation has been communicated to the next health care providers	Did the discharge summary specify the changes to medications?
1	☐YES – confirmed meds ☐YES – clarified one or more medications ☐NO ☐N/A - No admission Meds	☐LTC or RH ☐Home with home care ☐Home without care ☐Another Acute care facility ☐Other	☐YES ☐NO ☐N/A - No admission or discharge Meds	☐YES ☐NO ☐No Admission BPMH ☐N/A - No Home Meds on admission	☐YES – discrepancies involved high risk meds, specify: _____ ☐YES - discrepancies involved non-high risk meds, specify:_____ ☐NO	☐YES ☐NO	☐YES ☐NO ☐N/A - No Changes to BPMH Meds	☐YES ☐NO ☐Not Documented	☐YES – pharmacy ☐YES – family physician ☐YES - other ☐NO ☐Not Documented	☐YES – accurate ☐YES, but with ___ medication errors ☐No
2	☐YES – confirmed meds ☐YES – clarified one or more medications ☐NO ☐N/A - No admission Meds	☐LTC or RH ☐Home with home care ☐Home without care ☐Another Acute care facility ☐Other	☐YES ☐NO ☐N/A - No admission or discharge Meds	☐YES ☐NO ☐No Admission BPMH ☐N/A - No Home Meds on admission	☐YES – discrepancies involved high risk meds, specify: _____ ☐YES - discrepancies involved non-high risk meds, specify:_____ ☐NO	☐YES ☐NO	☐YES ☐NO ☐N/A - No Changes to BPMH Meds	☐YES ☐NO ☐Not Documented	☐YES – pharmacy ☐YES – family physician ☐YES - other ☐NO ☐Not Documented	☐YES – accurate ☐YES, but with ___ medication errors ☐No
3	☐YES – confirmed meds ☐YES – clarified one or more medications ☐NO ☐N/A - No admission Meds	☐LTC or RH ☐Home with home care ☐Home without care ☐Another Acute care facility ☐Other	☐YES ☐NO ☐N/A - No admission or discharge Meds	☐YES ☐NO ☐No Admission BPMH ☐N/A - No Home Meds on admission	☐YES – discrepancies involved high risk meds, specify: _____ ☐YES - discrepancies involved non-high risk meds, specify:_____ ☐NO	☐YES ☐NO	☐YES ☐NO ☐N/A - No Changes to BPMH Meds	☐YES ☐NO ☐Not Documented	☐YES – pharmacy ☐YES – family physician ☐YES - other ☐NO ☐Not Documented	☐YES – accurate ☐YES, but with ___ medication errors ☐No

Figure 1. Revised discharge medication reconciliation quality audit tool, with one row per patient (additional rows can be added as needed). BPMDP = best possible medication discharge plan, BPMH = best possible medication history, LTC = long-term care, MAR = medication administration record, N/A = not available, RH = retirement home.

Table 2. Results of Chart Audit and Interviews

Element of Chart Audit or Interview	No. (%) of Participants (*n* = 35*)
Chart audit	
BPMH clarified admission medications or doses	
Yes	7 (20)
No	4 (11)
NA (no BPMH completed by care team)	24 (69)
Discharge MedRec was performed	
Yes: discharge MedRec noted in chart	1 (3)
No: discharge prescription only	32 (91)
No: neither discharge MedRec nor discharge prescription provided	2 (6)
Sources of information used for discharge prescription	
Medication administration record	17 (49)
Not stated	16 (46)
NA	2 (6)
Unexplained differences between reconstructed BPMH and BPMDP	
Yes: involving high-risk medications	9 (26)
Yes: not involving high-risk medications	13 (37)
No	11 (31)
NA	2 (6)
Each medication on discharge prescription has drug name, dose, route, frequency	
Yes	31 (89)
No	2 (6)
NA	3 (4)
Discharge summary specifies medication changes	
Yes	17 (49)
No	18 (51)
Rationale for medication changes documented	
Yes	6 (17)
No	26 (74)
NA	3 (9)
Interviews	
Patient noted problems with medications in hospital (n = *31 patients)*	
Yes	8 (26)
No	21 (68)
Can't remember	2 (6)
Medications were discussed at discharge (n = *31 patients)*	
Yes, and was useful	13 (42)
Yes	7 (23)
No, would have been useful to discuss	4 (13)
No	6 (19)
Can't remember	1 (3)
Pharmacy received discharge prescription (n = *35 pharmacists)*	
Yes	28 (80)
No	5 (14)
NA (no discharge prescription provided to patient)	2 (6)
Pharmacist had to clarify discharge prescription (n = *35 pharmacists)*	
Yes	10 (29)
No	18 (51)
NA (no discharge prescription received)	7 (20)
Discharge documentation was received by family physician (n = *32 physicians)*	
Both discharge prescription and discharge summary	7 (22)
Discharge prescription only	3 (9)
Discharge summary only	18 (56)
Don't know	4 (13)
Family physician had to clarify discharge prescription (n = *32 physicians)*	
Yes	3 (9)
No	20 (63)
Can't remember	9 (28)

BPMH/BPMDP = best possible medication history/discharge plan, MedRec = medication reconciliation, NA = not applicable.
*Except where indicated otherwise.

at discharge were met for only 1 patient. Nonetheless, 13 (42%) of those interviewed felt that the limited discussion had been useful.

All 35 community pharmacists (100%) were interviewed. Five (14%) of the pharmacists noted that they had not received the discharge prescription that was prepared for the patient. Two recalled that the patient involved had deliberately withheld the new prescription because of changes made during the hospital stay (decrease in dose of opioids, discontinuation of benzodiazepines). The pharmacists noted problems that required clarification in 10 (36%) of the 28 discharge prescriptions received.

Thirty-two (91%) of the patients had family physicians, each of whom was interviewed. Twenty-eight (88%) of these family physicians had received discharge documents from the hospital, but only 10 (31%) had received a copy of the discharge prescription. Three (11%) of the 28 physicians with discharge documents of some kind reported confusion about the discharge prescription, and 2 (7%) had restarted medications that they did not realize had been stopped in hospital.

DISCUSSION

This study was the first evaluation of the discharge MedRec quality audit tool. Once modified to include information about the admission MedRec and more detailed information about discrepancies, the modified tool was thought to be highly useful for assessing the quality of the discharge MedRec. We found that an accurate discharge MedRec relied on an accurate BPMH and documentation of patient information influencing medication choices and doses (e.g., renal function, allergies). Following up with patients and their community providers after discharge added valuable additional information, primarily showing that the level of communication expected in a high-quality discharge MedRec was lacking. In addition, we uncovered a few examples of patients deliberately disrupting discharge prescription updates to their medications (by not taking the discharge prescription to their pharmacy) to regain access to high doses of opioids or benzodiazepines. As well, family physicians were unwittingly restarting medications that had been stopped while the patient was in hospital, a practice with potentially adverse clinical outcomes. Both of these types of miscommunication could have been avoided by transmitting the discharge prescription with full reconciliation directly to community care providers. Analyses of discharge MedRec have identified frequent medication discrepancies at the time of discharge[33], and the "silos" of Canadian health care do not facilitate seamless postdischarge MedRec.

Our study had several limitations, including the small sample size, the single large community, and the retrospective design. For many patients, we had to reconstruct the BPMH, which may have led to errors, particularly given that some patients take their medications quite differently from instructions on the prescription label. Despite these limitations, our pilot was informative on

3 main fronts. First, the proposed discharge MedRec quality audit tool had some significant gaps, but once these were addressed, the modified tool was easy to use and had good face validity. Second, application of the tool identified major limitations in the quality of discharge MedRec, often beginning with no or limited admission MedRec. Third, direct postdischarge communication with key stakeholders in the community, starting with sending a copy of the discharge prescription directly to the community pharmacy and to the patient's primary care provider, is necessary to avoid unintended or intended medication errors.

CONCLUSION

The modified discharge MedRec audit tool can aid in the improvement of hospital discharge MedRec processes nationally by serving as a quality checklist or reminder of process steps. Further research is needed to improve the efficiency of this potentially time-consuming and costly process and to evaluate whether a high-quality discharge MedRec process can improve patient outcomes or be cost-effective on its own or as a component of expert medication management. Several ongoing randomized trials are testing the effectiveness of expert medication management in the transition period from hospital to home.[34,35]

References

1. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. *Qual Saf Health Care.* 2008;17(3):216-23.
2. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-9.
3. Zed PJ, Abu-Laban RB, Balen RM, Loewen PS, Hohl CM, Brubacher JR, et al. Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. *CMAJ.* 2008;178(12):1563-9.
4. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ*. 2004;170(11):1678-86.
5. Kohn L, Corrigan J, Donaldson M. *To err is human: building a safer health system*. Washington (DC): National Academy Press; 1999.
6. Elliott R, Camacho E, Campbell F, Jankovic D, Martyn St James M, Kaltenthaler E, et al. *Prevalence and economic burden of medication errors in the NHS in England. Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK.* Sheffield and York (UK): Universities of Sheffield and York, Policy Research Unit in Economic Evaluation of Health and Care Interventions; 2018.
7. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. ADE Prevention Study Group. *JAMA*. 1995; 274(1):29-34.
8. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. *CMAJ*. 2005;173(5):510-5.
9. *Medication without harm*. Geneva (CH): World Health Organization; 2017 [cited 2018 Nov 19]. Available from: http://www.who.int/iris/handle/10665/255263
10. Boockvar KS, Blum S, Kugler A, Livote E, Mergenhagen KA, Nebeker JR, et al. Effect of admission medication reconciliation on adverse drug events from admission medication changes. *Arch Intern Med.* 2011;171(9):860-1.
11. Hellstrom LM, Bondesson A, Höglund P, Eriksson T. Errors in medication history at hospital admission: prevalence and predicting factors. *BMC Clin Pharmacol*. 2012;12:9.
12. Belda-Rustarazo S, Cantero-Hinojosa J, Salmeron-García A, González-García L, Cabeza-Barrera J, Galvez J. Medication reconciliation at admission and discharge: an analysis of prevalence and associated risk factors. *Int J Clin Pract*. 2015;69(11):1268-74.
13. Rodríguez Vargas B, Delgado Silveira E, Iglesias Peinado I, Bermejo Vicedo T. Prevalence and risk factors for medication reconciliation errors during hospital admission in elderly patients. *Int J Clin Pharm*. 2016;38(5):1164-71.
14. Ashcroft DM, Lewis PJ, Tully MP, Farragher TM, Taylor D, Wass V, et al. Prevalence, nature, severity and risk factors for prescribing errors in hospital inpatients: prospective study in 20 UK hospitals. *Drug Saf.* 2015;38(9): 833-43.
15. Holbrook A, Bowen JM, Patel H, O'Brien C, You JJ, Tahavori R, et al. Process mapping evaluation of medication reconciliation in academic teaching hospitals: a critical step in quality improvement. *BMJ Open*. 2016;6(12):e013663.
16. *The National Patient Experience Survey: findings of the 2017 inpatient survey.* National Patient Experience Survey [Ireland]; 2017 [cited 2018 Nov 14]. Available from: https://yourexperience.ie/wp-content/uploads/2019/07/NPES-National-Report-2017-WEB.pdf
17. Pippins JR, Gandhi TK, Hamann C, Ndumele CD, Labonville SA, Diedrichsen EK, et al. Classifying and predicting errors of inpatient medication reconciliation. *J Gen Intern Med*. 2008;23(9):1414-22.
18. Gleason KM, Groszek JM, Sullivan C, Rooney D, Barnard C, Noskin GA. Reconciliation of discrepancies in medication histories and admission orders of newly hospitalized patients. *Am J Health Syst Pharm*. 2004; 61(16):1689-95.
19. Wong JD, Bajcar JM, Wong GG, Alibhai SM, Huh JH, Cesta A, et al. Medication reconciliation at hospital discharge: evaluating discrepancies. *Ann Pharmacother*. 2008;42(10):1373-9.
20. Shiu JR, Fradette M, Padwal RS, Majumdar SR, Youngson E, Bakal JA, et al. Medication discrepancies associated with a medication reconciliation program and clinical outcomes after hospital discharge. *Pharmacotherapy.* 2016;36(4):415-21.
21. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. *Cochrane Database Syst Rev.* 2016;2: CD008986.
22. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. *Cochrane Database Syst Rev.* 2018;8:CD010791.
23. Urban R, Armitage G, Morgan J, Marshall K, Blenkinsopp A, Scally A. Custom and practice: a multi-center study of medicines reconciliation following admission in four acute hospitals in the UK. *Res Social Admin Pharm.* 2014;10:355-68.
24. *Required organizational practices: handbook 2017*. Version 2. Ottawa (ON): Accreditation Canada; 2017 [cited 2019 Oct 31]. Available from: https://www3.accreditation.ca/OrgPortal/Documents/Resources/AddResources/ROPHandbook_2017_v2_EN.pdf
25. *National patient safety goals effective January 2019: hospital accreditation program*. Oakbrook Terrace (IL): The Joint Commission; 2019 [cited 2019 Oct 31]. Available from: https://www.jointcommission.org/assets/1/6/NPSG_Chapter_HAP_Jan2019.pdf
26. *NICE Guideline NG5: Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes.* London (UK): National Institute for Health and Care Excellence; 2015 [cited 2018 Sep 26]. Available from: nice.org.uk/guidance/ng5
27. Ravn-Nielsen L, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: a randomized clinical trial. *JAMA Intern Med.* 2018;178(3):375-82.
28. *Medication reconciliation (MedRec)*. Toronto (ON): Institute for Safe Medication Practices Canada; © 2008–2019 [cited 2018 Nov 14]. Available from: https://www.ismp-canada.org/medrec/
29. *Medication reconciliation in acute care. Getting started kit.* Version 4. Canadian Patient Safety Institute and Institute for Safe Medication Practices Canada; 2017 [cited 2018 Nov 14]. Available from: https://www.ismp-canada.org/download/MedRec/MedRec-AcuteCare-GSK-EN.pdf
30. *Measures: medication reconciliation (MedRec).* Edmonton (AB): Canadian Patient Safety Institute (CPSI); [cited 2018 Nov 26]. Available from: http://www.patientsafetyinstitute.ca/en/toolsresources/psm/pages/medrec-measurement.aspx

31. *Drug profile viewer* [website]. Toronto (ON): eHealth Ontario; [cited 2016 Mar 3]. Available from: http://www.ehealthontario.on.ca/en/initiatives/view/drug-profile-viewer
32. *High-alert medications in community/ambulatory settings*. Horsham (PA): Institute for Safe Medication Practices; 2011 Jan 31 [cited 2018 Nov 14]. Available from: https://www.ismp.org/recommendations/high-alert-medications- community-ambulatory-list
33. Michaelsen MH, McCague P, Bradley CP, Sahm LJ. Medication reconciliation at discharge from hospital: a systematic review of the quantitative literature. *Pharmacy (Basel)*. 2015;3(2):53-71.
34. Clinical Trials.gov identifier NCT027770472016: Anticoagulant safety at hospital discharge [clinical trial registration]. Bethesda (MD): US National Library of Medicine, ClinicalTrials.gov; 2016 [cited 2018 Sep 26]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02777047?cond=anticoagulants&rank=2
35. Clinical Trials.gov identifier NCT04077281: Improving Medication Prescribing-Related Outcomes for Vulnerable Elderly In Transitions (IMPROVE-IT) [clinical trial registration]. Bethesda (MD): US National Library of Medicine, ClinicalTrials.gov; 2019 [cited 2019 Nov 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT04077281?term=IMPROVE-IT&recrs=b&draw=2&rank=1

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ON THE FRONT COVER

Columbia Icefield
Jasper National Park, Alberta

Benton Attfield took the cover photo of a sundog in February 2017, at a location south of the Columbia Icefield in Jasper National Park, using a Canon PowerShot SX270 HS camera. Benton is a clinical pharmacist in the Emergency Department at Foothills Medical Centre in Calgary, Alberta. His practice areas of interest include addictions medicine, toxicology, and patient transitions of care. In addition to adventuring in the great outdoors on foot or bike, he enjoys cooking and exploring new cuisines.

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.pharmacy.

ORIGINAL RESEARCH

Anticoagulant Utilization and Direct Oral Anticoagulant Prescribing in Patients with Nonvalvular Atrial Fibrillation

Priscilla Shum, Gordon Klammer, Dale Toews, and Arden Barry

ABSTRACT

Background: Direct oral anticoagulants (DOACs) are indicated for prevention of stroke and embolism in patients with nonvalvular atrial fibrillation (NVAF). These agents have been shown to be non-inferior to warfarin in terms of efficacy and safety. However, their uptake in practice has been variable, and prescribed dosages may be inconsistent with manufacturer recommendations.

Objectives: To evaluate patterns of oral anticoagulant use in patients with NVAF, including determination of patient characteristics associated with the prescribing of warfarin or DOACs and whether prescribed dosages of DOACs were concordant with manufacturer recommendations.

Methods: This retrospective chart review was conducted from April to September 2017 at Abbotsford Regional Hospital, Abbotsford, British Columbia. Patients at least 18 years of age with NVAF and CHADS-65 score of 1 or higher were included. Patients with contraindications to oral anticoagulants, those with reversible atrial fibrillation, and those undergoing renal dialysis were excluded. The dosage of DOACs was categorized as too low, too high, or correct in relation to manufacturer recommendations for the Canadian product.

Results: A total of 120 patients were included. At discharge, 83 (69%) of the patients had a prescription for DOAC, 25 (21%) had a prescription for warfarin, and 12 (10%) had no prescription for an oral anticoagulant. There were no statistically significant differences between the warfarin and DOAC groups with respect to patient characteristics. Among the 56 patients for whom a full DOAC dose was indicated, 7 (13%) received a dose that was too low. Among the 23 patients for whom a full DOAC dose was not indicated, 4 (17%) received a dose that was too high.

Conclusions: At the study hospital, most patients with NVAF and CHADS-65 score of at least 1 had a discharge prescription for DOAC. Patient characteristics appeared to be similar between the warfarin and DOAC groups. For a notable proportion of patients who received a DOAC, the dosage was incorrect. Appropriate prescribing of oral anticoagulants could be further improved by education for prescribers and involvement of hospital pharmacists.

RÉSUMÉ

Contexte : Les anticoagulants oraux directs (AOD) sont indiqués pour prévenir les AVC et les embolies parmi les patients atteints de fibrillation auriculaire non valvulaire (FANV). Il a été démontré que l'efficacité et l'innocuité de ces agents n'étaient pas inférieures à la warfarine. Cependant, leur adoption dans la pratique est inégale, et les doses prescrites peuvent être contraires aux recommandations des fabricants.

Objectifs : Évaluation des habitudes d'utilisation des anticoagulants oraux pour les patients atteints de FANV, y compris la définition des caractéristiques des patients associées à la prescription de la warfarine ou des AOD, ainsi que de la conformité des doses prescrites de ces derniers aux recommandations des fabricants.

Méthodes : Cet examen rétrospectif des dossiers a été mené d'avril à septembre 2017 à l'Hôpital régional d'Abbotsford à Abbotsford, en Colombie-Britannique. Des patients âgés d'au moins 18 ans, atteints de FANV et ayant un score CHADS-65 d'au moins 1, ont été inclus dans l'étude. Les patients présentant une contre-indication aux anticoagulants oraux, ceux atteints de fibrillation auriculaire réversible et ceux soumis à une dialyse rénale en ont été exclus. La dose d'AOD destinés au marché canadien a été catégorisée comme trop faible, trop élevée ou correcte par rapport aux recommandations du fabricant.

Résultats : Cent-vingt patients au total ont participé à l'étude. Au moment du congé, 83 (69 %) d'entre eux avaient une prescription d'AOD, 25 (21 %) avaient une prescription de warfarine et 12 (10 %) n'avaient pas de prescription d'anticoagulant oral. En ce qui concerne les caractéristiques des patients, il n'y avait aucune différence statistique notable entre les groupes ayant reçu une prescription de warfarine et ceux ayant reçu une prescription d'AOD. Des 56 patients qui avaient reçu une indication de dose complète d'AOD, sept (13 %) ont reçu une dose trop faible. Des 23 patients qui n'avaient pas reçu d'indication de dose complète d'AOD, quatre (17 %) ont reçu une dose trop élevée.

Conclusions : À l'hôpital où s'est déroulée l'étude, la plupart des patients atteints de FANV et ceux ayant un score CHADS-65 d'au moins 1 recevaient une prescription d'AOD au moment du congé. Les caractéristiques des patients semblaient similaires entre les groupes ayant reçu une

Keywords: atrial fibrillation, stroke, anticoagulants, medical records, retrospective studies

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prescription de warfarine et ceux ayant reçu une prescription d'AOD. La dose d'AOD reçue par une proportion notable de patients était incorrecte. La prescription appropriée d'anticoagulants oraux pourrait encore être améliorée si on sensibilisait les prescripteurs avec la collaboration des pharmaciens d'hôpitaux.

Mots-clés: fibrillation auriculaire, AVC, anticoagulants, dossiers médicaux, examen rétrospectif

INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia in North America, affecting approximately 200 000 Canadians in 2018.[1] The formation of atrial thrombi, which can occur with any type of atrial fibrillation, may result in ischemic stroke, the most common manifestation of embolization.[2] In use since the 1950s, warfarin is a vitamin K antagonist indicated for prevention of stroke in patients with atrial fibrillation.[3] Trials have demonstrated that warfarin is effective in reducing the risk of stroke by two-thirds relative to placebo, as well as showing superiority when compared with the combination of acetylsalicylic acid (ASA) and clopidogrel.[3,4] Despite the efficacy of warfarin, its use is limited by its narrow therapeutic range, the need for frequent monitoring of international normalized ratio (INR) and corresponding dose adjustments, and many drug-drug and drug-food interactions.[5-7]

Since 2010, four direct oral anticoagulants (DOACs)—apixaban, dabigatran, edoxaban, and rivaroxaban—have been approved in Canada for prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF).[5-7] This form of atrial fibrillation is defined as atrial fibrillation not associated with rheumatic mitral stenosis of any severity, moderate-to-severe nonrheumatic mitral stenosis, or mechanical heart valves.[6] Relative to warfarin, DOACs offer therapeutic and lifestyle advantages, including rapid onset and offset of action, no requirement for INR monitoring, fewer drug-drug and drug-food interactions, and fewer lifestyle modifications.[5-7] The landmark trials for DOACs, specifically RE-LY,[8] ROCKET-AF,[9] ARISTOTLE,[10] and ENGAGE AF-TIMI 48,[11] have shown that all 4 DOACs are at least noninferior to warfarin in the reduction of stroke and systemic embolism. There was also a reduction in hemorrhagic stroke and intracranial hemorrhage with all 4 DOACs relative to warfarin.[8-11] None of the DOACs were associated with an increase in major bleeding, but there was an increase in gastrointestinal bleeding events associated with dabigatran (at 150 mg twice daily), rivaroxaban, and edoxaban (at 60 mg once daily).[8-11] Postmarketing, real-world data pertaining to the efficacy and safety of DOACs have been consistent with the landmark trials.[12] The current atrial fibrillation guidelines of the Canadian Cardiovascular Society (CCS) endorse the preference for DOACs over warfarin in patients with a CHADS-65 score of 1 or higher.[6] The DOACs are also recommended as suitable alternatives to warfarin in the atrial fibrillation guidelines of both the American Heart Association (published in 2014)[5] and the European Society of Cardiology (published in 2016).[7]

Around the world, uptake of DOACs in practice has been variable. In Canada, a population-based descriptive analysis from Ontario demonstrated rapid uptake of DOACs within 2 years after approval.[13] Over a 24-month period (October 2010 to September 2012), there was a 20-fold increase in DOAC prescriptions, accounting for 21% of all anticoagulant prescriptions.[13] In contrast, a prospective survey using the European EORP-AF (EURObservational Research Programme Atrial Fibrillation) registry showed that of the 3119 patients enrolled, 72% received warfarin, but only 8% received a DOAC.[14] Furthermore, several recent studies of DOAC prescribing in practice have shown that prescribed doses are often inconsistent with the manufacturer's recommendations.[15,16] In a study of dabigatran utilization in the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), more than half of the patients with severe kidney disease did not receive the recommended reduced dose, whereas 10% of those with normal renal function received a dose that was lower than recommended.[15] Similarly, in a recently published study by Yao and others,[16] of the approximately 1500 patients with an indication for renal adjustment of DOAC dose, 43% received standard dosages. In contrast, among roughly 13 000 patients with no indication for renal adjustment of DOAC dose, 13% may have received a dose that was too low.[16]

The purpose of this study was to describe and evaluate the local prescribing patterns of anticoagulant therapy in patients with NVAF at the Abbotsford Regional Hospital (ARH) located in Abbotsford, British Columbia. This was a quality assurance project to ensure safe and effective prescribing of oral anticoagulants for patients in the ARH region. In addition, patient characteristics associated with the use of warfarin or a DOAC were evaluated, as well as the concordance of DOAC prescribing with manufacturer recommendations.

METHODS

This single-centre retrospective study involved review of electronic medical records. Health records personnel identified patients admitted to the ARH between April 1, 2017, and September 30, 2017, who had a documented diagnosis of atrial fibrillation, based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) coding. This study was deemed to be a quality assurance project and thus exempt from full review by the ARH Research Ethics Board.

Study Population

Patients aged 18 years or older with an indication for long-term oral anticoagulation (defined as CHADS-65 score ≥ 1) were included. On the basis of information documented in the admission consultation notes and discharge summary, patients were excluded if they had mitral stenosis or a mechanical heart valve, a contraindication to taking an oral anticoagulant (e.g., hypersensitivity, active intracranial bleeding, pregnancy), a left atrial appendage exclusion device, or atrial fibrillation due to reversible causes, or if they were receiving renal dialysis. If a patient had multiple admissions within the study period, only the most recent eligible admission was included.

Data Collection

A standardized data collection form was used. Most of the data collection was performed by one investigator (P.S.), for consistency. Data for the following patient characteristics were collected: demographic and physical characteristics (age, sex, weight), anticoagulant prescribed on discharge (apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, or none), components of the CHADS-65 score, components of the HAS-BLED score, and other medical conditions. Components of the CHADS-65 score were heart failure; hypertension; age older than 65 years; diabetes mellitus; and a history of ischemic stroke, transient ischemic attack, or arterial thromboembolism.[6] Heart failure was defined, in accordance with the CCS,[6] as moderate-to-severe systolic dysfunction, signs and symptoms of heart failure with reduced ejection fraction, or recent decompensated heart failure that required hospitalization irrespective of ejection fraction. Components of the HAS-BLED score were uncontrolled hypertension (systolic blood pressure > 160 mm Hg), abnormal renal function (long-term dialysis, renal transplant, or serum creatinine ≥ 200 µmol/L), abnormal liver function (cirrhosis; bilirubin greater than 2 times the upper limit of normal; or aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase greater than 3 times the upper limit of normal), history of ischemic or hemorrhagic stroke, history of gastrointestinal bleeding or other major bleeding (excluding hemorrhagic stroke), age older than 65 years, use of nonsteroidal anti-inflammatory drugs or antiplatelet agent (ASA, clopidogrel, prasugrel, or ticagrelor), and excessive alcohol use (> 8 drinks per week).[17] The CHADS-65 and HAS-BLED scores were calculated using the available data collected, with the exception of labile INR and anemia for the HAS-BLED score, as it was not feasible to reliably collect these data from the medical records. Uncontrolled hypertension was based on the last reading before discharge. Major bleeding was defined as bleeding that led to hospitalization, a decrease in hemoglobin of more than 20 g/L, or a need for transfusion. The DOAC dose was assessed as too low, too high, or correct in relation to the manufacturer's recommendations for the Canadian product. In accordance with recommendations in the European Heart Rhythm Association's practical guide on the use of new oral anticoagulants in patients with NVAF, common drug interactions were also taken into account to determine whether adjustment of the DOAC dose was warranted.[18]

Statistical Analysis

Prescribing patterns were described using proportions. Patient characteristics were described using proportions with 95% confidence intervals for categorical variables and means with standard deviations for continuous variables. Baseline characteristics of patients using warfarin and DOACs were compared using a χ^2 test for categorical variables (or the Fisher exact test if the number of patients was less than 5) or the Student t test for continuous variables (or the Welch t test if there was unequal variance between groups). A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 184 patients were identified, of whom 120 were included in the study (Figure 1). The most common reasons for exclusion were a CHADS-65 score less than 1 and atrial fibrillation due to reversible causes. There was a higher proportion of men in the warfarin group, and patient weight was numerically higher in the group receiving no oral anticoagulant (Table 1). The mean CHADS-65 score was comparable across all 3 groups, and the mean HAS-BLED score was numerically higher in the group receiving no oral anticoagulant. This group also had a higher proportion of patients receiving either ASA or a P2Y12 inhibitor. However, there were no statistically significant differences between the warfarin and DOAC groups with respect to patient characteristics, comorbid medical conditions, or mean CHADS-65 and HAS-BLED scores. An analysis comparing the no oral anticoagulant group to the other groups was not performed because of the low number of patients in that group.

At discharge, most patients (83/120, 69%) had a prescription for a DOAC, and 25 (21%) had a prescription for warfarin (Figure 2). Twelve (10%) of the patients had no prescription for an oral anticoagulant at discharge. The most commonly prescribed DOACs were apixaban (42 [35%] of the 120 patients

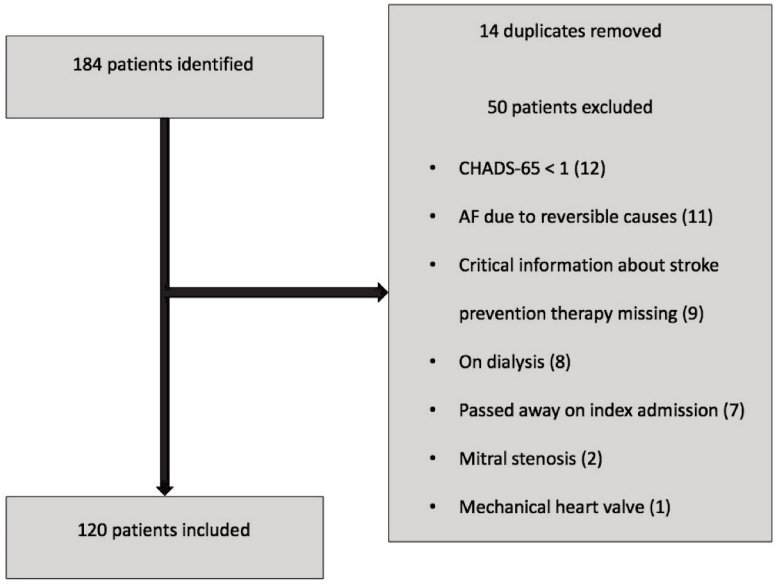

Figure 1. Flow chart showing patient selection for a study of oral anticoagulants in patients with nonvalvular atrial fibrillation (AF).

in the study) and rivaroxaban (38/120, 32%). Only 3 (2%) of the patients had a prescription for dabigatran, and none were receiving edoxaban. Among patients without a prescription for an oral anticoagulant, only 7 had a documented reason: 3 declined to take an oral anticoagulant, 1 had a recent episode of gastrointestinal bleeding, 1 had a recent episode of retroperitoneal bleeding, and 2 were considered to be at high risk of falling.

With respect to DOAC prescribing, data were available for 79 of the 83 patients. A full dose was indicated for most of the patients (56/79, 71%) (Figure 3). Of these patients, 49 (87%) had the correct dosage prescribed, whereas the remaining 7 (13%) had a prescribed dosage that was too low. Of the patients for whom a full dose was not indicated (23/79, 29%), 19 (83%) had the correct dosage prescribed, whereas the remaining 4 (17%) had a prescribed dosage that was too high. Of these latter 4 patients, 3 required dose adjustment on the basis of renal function. The fourth patient was taking itraconazole, which—according to Canadian manufacturer's recommendations—is a contraindication to DOAC therapy.

DISCUSSION

In the study institution, more than two-thirds of patients with a diagnosis of NVAF had a prescription for a DOAC at discharge, in alignment with the current CCS guideline for atrial fibrillation.[6] The most commonly prescribed DOACs were apixaban and rivaroxaban. No patients were receiving edoxaban, probably because it is not currently listed on the ARH hospital formulary and is not eligible for provincial drug coverage.

However, 12 patients (10%) had no prescription for an oral anticoagulant at discharge. Compared with those for whom warfarin or a DOAC was prescribed, these patients had a numerically higher mean HAS-BLED score; therefore, their risk of bleeding may have been the reason no oral anticoagulant was prescribed. In addition, a higher proportion of these patients were taking ASA or a P2Y12 inhibitor, drugs that offer some protection against stroke or systemic embolism in patients with atrial fibrillation. However, ASA monotherapy or ASA in combination with clopidogrel have been shown to be inferior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation.[3,4] In addition, the combination of ASA and clopidogrel was associated with a risk of bleeding similar to that of warfarin.[4] In one case in this study, a high risk of falling was documented as the reason for not prescribing an oral anticoagulant, which may not have been appropriate. In older patients who have a 5% annual risk for stroke (i.e., CHADS-65 score of approximately 2–3) and who are taking an oral anticoagulant, an analytical model estimated that a patient would have to fall 295 times per year to sustain a subdural hemorrhage.[19] Therefore, the authors concluded that for most patients, the risk of falling while receiving anticoagulant therapy likely does not exceed the benefit of taking an anticoagulant.

Prescribing of oral anticoagulants for patients with NVAF could be improved at the ARH through means such as education for prescribers and involvement of hospital pharmacists. Targeted education could be offered to prescribers regarding the relative benefits and risks of oral anticoagulant therapy. Such education could help to address common misconceptions about the

Table 1. Baseline Characteristics of Patients

Characteristic	Drug Therapy Group; No. (%) of Patients*			*p* value†
	Warfarin (*n* = 25)	DOAC (*n* = 83)	No OAC (*n* = 12)	
Age (years) (mean ± SD)	78 ± 8.6	79 ± 11.6	78 ± 10.8	0.55
Sex, male	17 (68)	43 (52)	6 (50)	0.15
Weight (kg) (mean ± SD)	84.5 ± 29.5	78.5 ± 25.3	89.3 ± 15.6	0.34
Kidney function				
Serum creatinine (μmol/L) (mean ± SD)	116 ± 69.4	93 ± 29.3	99.6 ± 34.9	0.12
eGFR (mL/min) (mean ± SD)	59 ± 22.1	63.2 ± 20.2	61.2 ± 26.8	0.38
Liver function				
ALT/AST/ALP > 3x ULN	0 (0)	3 (4)	2 (17)	0.90
Total bilirubin > 2x ULN	3 (12)	4 (5)	0 (0)	0.20
Concurrent medications				
NSAID	0 (0)	1 (1)	0 (0)	0.90
ASA	3 (12)	12 (14)	10 (83)	0.90
P2Y12 inhibitor	1 (4)	5 (6)	4 (33)	0.90
Comorbidities				
Hypertension	20 (80)	62 (75)	8 (67)	0.59
Heart failure	15 (60)	35 (42)	4 (33)	0.12
Ischemic stroke/TIA	6 (24)	21 (25)	2 (17)	0.90
Stable CAD	7 (28)	15 (18)	2 (17)	0.28
ACS (≤1 year)	0 (0)	7 (8)	1 (8)	0.20
Arterial thromboembolism	0 (0)	0 (0)	0 (0)	NA
Hemorrhagic stroke	0 (0)	0 (0)	1 (8)	NA
Gastrointestinal bleed	0 (0)	2 (2)	1 (8)	0.90
Other major bleed	0 (0)	1 (1)	3 (25)	0.90
Diabetes mellitus	8 (32)	19 (23)	3 (25)	0.36
CKD (stage 2–5)	10 (40)	35 (42)	6 (50)	0.85
Renal transplant	0 (0)	0 (0)	0 (0)	NA
Liver cirrhosis	0 (0)	0 (0)	0 (0)	NA
Current alcohol misuse	1 (4)	4 (5)	0 (0)	0.90
Scores				
CHADS-65 score (mean ± SD)	3.1 ± 1.1	2.8 ± 1.2	2.6 ± 1.1	0.30
HAS-BLED score (mean ± SD)	1.6 ± 0.8	1.5 ± 0.8	2.5 ± 0.5	0.87

ACS = acute coronary syndrome, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ASA = acetylsalicylic acid, AST = aspartate aminotransferase, CAD = coronary artery disease, CKD = chronic kidney disease, DOAC = direct-acting oral anticoagulant, eGFR = estimated glomerular filtration rate, NSAID = nonsteroidal anti-inflammatory drug, OAC = oral anticoagulant, SD = standard deviation, TIA = transient ischemic attack, ULN = upper limit of normal.
*Except where indicated otherwise.
†For comparison of patients receiving warfarin with patients receiving DOAC by χ^2 test, Fisher exact test, Student *t* test, or Welch *t* test.

contraindications to oral anticoagulant therapy, such as a patient's risk of falling. A pharmacist-led initiative aimed at improving the prescribing of oral anticoagulants might help to ensure that all patients with NVAF are appropriately assessed for oral anticoagulation, and might also improve documentation to ensure continuity of care and increase awareness among prescribers about pharmacists' ability to address drug therapy issues. Drug therapy issues that hospital pharmacists could help to resolve might include inappropriate prescribing, absence of an approved indication, presence of a contraindication, potential drug-drug and drug-disease interactions, concerns about patient adherence or medication cost, patients' inability to take oral medication, and identification of other clinical considerations (e.g., use of DOACs in patients with obesity or severe renal dysfunction).

Several studies that evaluated oral anticoagulant prescribing patterns have identified patient-specific factors that may influence the prescribing of warfarin in preference to DOACs.[13,14,20-24] These factors include a history of gastrointestinal bleeding, older age, multiple comorbid medical conditions, and medication cost. At the ARH, it is likely that cost is a barrier only for a minority of patients who do not qualify for provincial drug coverage. To qualify for provincial drug coverage, patients must have had labile INR with warfarin therapy over a 2-month trial period or an inability to monitor INR regularly.[25] This criterion permits most patients to qualify for provincial drug coverage, and may be why warfarin was prescribed for fewer than one-quarter of patients. When patient characteristics were compared between those with

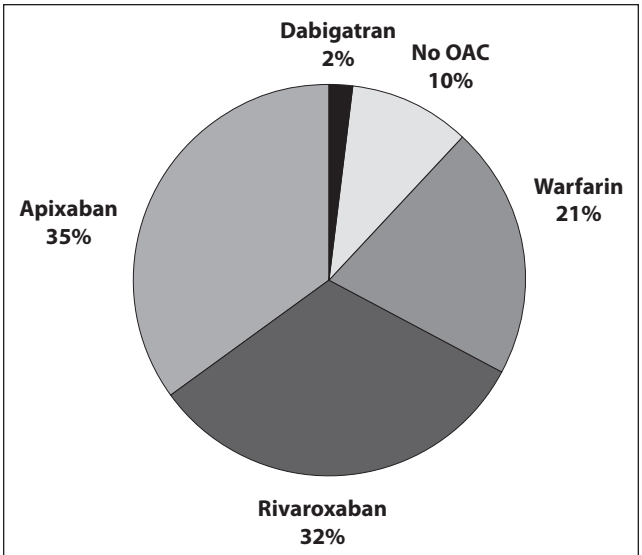

Figure 2. Primary outcome: oral anticoagulant (OAC) regimen on discharge (n = 120).

a prescription for warfarin and those receiving a DOAC, no statistically significant differences were identified. However, this analysis may have been underpowered because of the small sample size. Further prospective studies assessing patients' and prescribers' perspectives may help to illuminate the rationale behind oral anticoagulant prescribing patterns.

In terms of DOAC prescribing in the present study, the incidence of patients receiving a higher-than-recommended dose was below that reported by Yao and others[16] (17% versus 43%, respectively). The study by Yao and others[16] took place in the United States, in a health care setting similar to the ARH region, so a greater similarity in results might have been expected. One possible explanation for the observed difference is increased familiarity with these medications among prescribers in the current study, given that data in the earlier study were obtained between 2010 and 2015. The incidence of patients receiving a lower-than-recommended dose was similar in the current study and the study by Yao and others[16] (12.5% versus 13%, respectively).

This study had several limitations that warrant discussion. First, it was a retrospective study, and thus relied on the accuracy and completeness of documentation in the medical records. As well, because of the small sample size, the study may have been underpowered to identify between-group differences. No statistical analysis was performed to compare the group receiving no oral anticoagulant with the other groups, because there were only a few patients who did not receive any oral anticoagulant. Finally, this study did not assess adherence or cost concerns, which might have affected prescribing patterns. As stated above, future prospective studies may help to further clarify prescribing patterns.

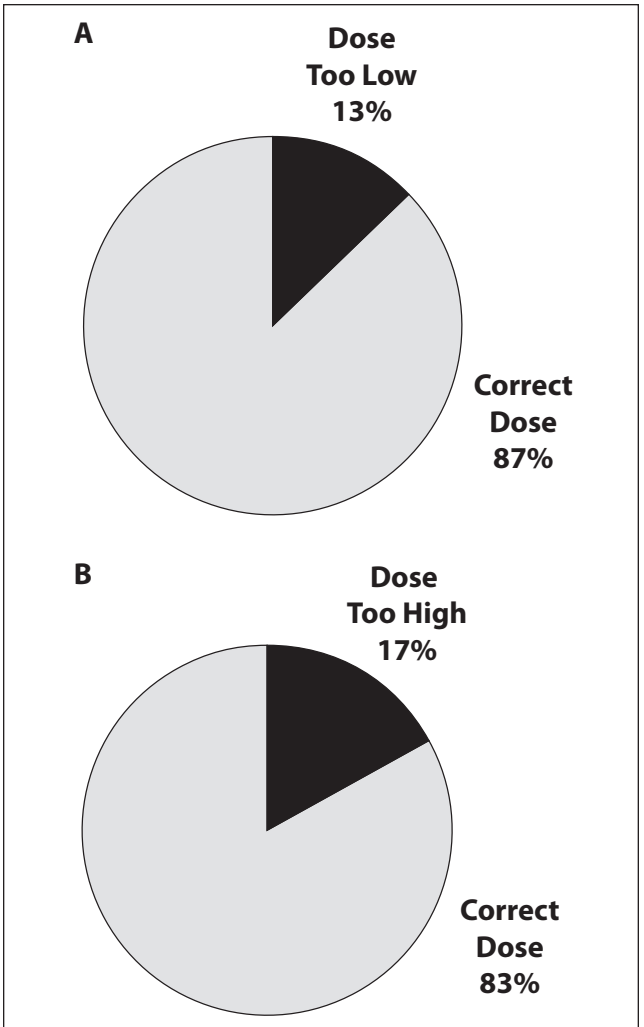

Figure 3. Secondary outcome: prescribing of direct-acting oral anticoagulants in (A) patients for whom a full dose was indicated (n = 56) and (B) patients for whom a full dose was not indicated (n = 23).

CONCLUSION

At the ARH, more than two-thirds of patients with NVAF and a CHADS-65 score of 1 or higher had a prescription for a DOAC at discharge, which aligns with the current CCS atrial fibrillation guideline recommendations. Patient characteristics were similar between those receiving warfarin and those receiving a DOAC, although this study was likely underpowered to observe any differences in these characteristics. For most of the patients with a discharge prescription for a DOAC, the drug was correctly prescribed, although 14% of the patients received a dose that was either too high or too low in relation to the manufacturer's recommendations. Prescribing of oral anticoagulants could likely be further improved by education of prescribers and involvement of hospital pharmacists.

References

1. *Atrial fibrillation*. Ottawa (ON): Heart and Stroke Foundation of Canada; 2018 [cited 2019 Nov 12]. Available from: https://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
2. Kim YH, Roh SY. The mechanism of and preventive therapy for stroke in patients with atrial fibrillation. *J Stroke*. 2016;18(2):129-37.
3. Hart R, Pearce L, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146(12):857-67.
4. Connolly SJ, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367(9526):1903-12.
5. January C, Wann L, Alpert J, Calkins H, Cigarroa J, Cleveland J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol.* 2014;64(21):e1-e76.
6. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, et al. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2016;32(10):1170-85.
7. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-962.
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51.
9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-91.
10. Granger CB, Alexander JH, McMurray JV, Lopes RD, Hylek E, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92.
11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-104.
12. Lee LH. DOACs - advances and limitations in real world. *Thromb J*. 2016;14(Suppl 1):17.
13. Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *CMAJ Open*. 2013;1(3):E115-9.
14. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16(3):308-19.
15. Steinberg BA, Holmes DN, Piccini JP, Ansell J, Chang P, Fonarow GC, et al. Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. *J Am Heart Assoc*. 2013;2(6):e000535.
16. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol.* 2017;69(23):2779-90.
17. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010; 138(5):1093-100.
18. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H, Hacke W, et al.; ESC Scientific Document Group. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J*. 2017;38(27):2137-49.
19. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med.* 1999;159(7):677-85.
20. AbuDagga A, Stephenson JJ, Fu AC, Kwong WJ, Tan H, Weintraub WS. Characteristics affecting oral anticoagulant therapy choice among patients with non-valvular atrial fibrillation: a retrospective claims analysis. *BMC Health Serv Res*. 2014;14:310.
21. Desai NR, Krumme AA, Schneeweiss S, Shrank WH, Brill G, Pezalla EJ, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation - quality and cost implications. *Am J Med.* 2014;127(11):1075-82.
22. Tagaya M, Yoshikawa D, Sugishita Y, Yamauchi F, Ito T, Kamada T, et al. Prescription patterns of oral anticoagulants for patients with non-valvular atrial fibrillation: experience at a Japanese single institution. *Heart Vessels.* 2016;31(6):957-62.
23. Brais C, Larochelle J, Turgeon M, Tousignant A, Blais L, Perreault S, et al. Patterns of oral anticoagulants use in atrial fibrillation. *J Popul Ther Clin Pharmacol.* 2015;22(1):e90-5.
24. Alamneh EA, Chalmers L, Bereznicki LR. Suboptimal use of oral anticoagulants in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices? *Am J Cardiovasc Drugs*. 2016;16(3): 183-200.
25. *Special authority request- apixaban/dabigatran/rivaroxaban for atrial fibrillation.* Victoria (BC): Ministry of Health; 2019 [cited 2019 Nov 12]. Available from: https://www2.gov.bc.ca/assets/gov/health/forms/5391fil.pdf

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Clinical Interventions to Prevent Tumour Lysis Syndrome in Hematologic Malignancy: A Multisite Retrospective Chart Review

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ABSTRACT

Background: Tumour lysis syndrome (TLS) occurs when lysis of malignant cells causes electrolyte disturbances and potentially organ dysfunction. Guidelines recommending preventive therapy according to TLS risk are based on low-quality evidence.

Objectives: The primary objective was to characterize utilization of TLS preventive strategies through comprehensive description of current practice. Secondary objectives were to determine TLS incidence, to compare use of preventive strategies among intermediate- and high-risk patients, and to describe TLS treatment strategies.

Methods: This retrospective chart review examined data for patients with newly diagnosed hematologic malignancy who were admitted to an oncology centre and/or affiliated intensive care unit between October 2015 and September 2016 in Toronto, Ontario, Canada.

Results: Fifty-eight patients (29 at intermediate risk, 29 at high risk) were eligible for inclusion. Use of preventive allopurinol, IV bicarbonate, and furosemide was similar between groups. Rasburicase was more frequently used for high-risk patients (3% [1/29] of intermediate-risk patients versus 36% [9/25] of high-risk patients; $p = 0.003$). In 4 (14%) of the intermediate-risk patients and 2 (8%) of the high-risk patients, TLS developed during the admission. TLS was observed in 10% (1/10) of patients who received preventive rasburicase and 11% (5/44) of those who did not ($p > 0.99$), and in 9% (4/45) of patients who received preventive IV bicarbonate and 25% (2/8) of those who did not ($p = 0.22$). Treatment strategies included rasburicase, IV bicarbonate, furosemide, and renal replacement therapy.

Conclusions: In this retrospective chart review, rasburicase was more commonly used for high-risk patients, whereas the use of other agents was similar between risk groups. This pattern of use is inconsistent with guidelines, which recommend that all high-risk patients receive rasburicase. There was no difference in TLS incidence between patients who did and did not receive preventive rasburicase or IV bicarbonate. Further prospective studies are needed to inform management of patients with malignancies who are at intermediate or high risk of TLS.

Keywords: tumour lysis syndrome, rasburicase, bicarbonate, allopurinol

RÉSUMÉ

Contexte : Le syndrome de lyse tumorale (SLT) se produit lorsque la lyse de cellules malignes provoque des perturbations électrolytiques et la dysfonction potentielle d'un organe. Les lignes directrices préconisant une thérapie préventive basée sur le risque de SLT se fondent sur des éléments de preuve de piètre qualité.

Objectifs : L'objectif principal consistait à décrire l'adoption des stratégies de prévention du SLT en décrivant précisément la pratique actuelle. Les objectifs secondaires consistaient, quant à eux, à déterminer l'incidence du SLT, à comparer l'utilisation des stratégies de prévention pour les patients présentant un risque élevé et moyen et à décrire les stratégies de traitement du SLT.

Méthodes : Cet examen rétrospectif a permis d'examiner les données de patients ayant récemment reçu un diagnostic d'hémopathie maligne et ayant été admis dans un centre d'oncologie ou une unité de soins intensifs affiliée, entre octobre 2015 et septembre 2016 à Toronto (Ontario), au Canada.

Résultats : Cinquante-huit patients (29 présentant un risque moyen et 29 un risque élevé) étaient admissibles. L'utilisation d'allopurinol à titre préventif, de bicarbonate par voie intraveineuse et de furosémide était similaire d'un groupe à l'autre. Le rasburicase était plus fréquemment utilisé pour les patients présentant un risque élevé (3 % [1/29] de patients présentant un risque moyen contre 36 % [9/25] de patients présentant un risque élevé; $p = 0.003$). Quatre (14 %) patients présentant un risque moyen et deux (8 %) présentant un risque élevé ont développé un SLT pendant l'admission. Le SLT a été observé chez 10 % (1/10) des patients ayant reçu du rasburicase à titre préventif et chez 11 % (5/44) des patients qui n'en avaient pas reçu ($p > 0{,}99$); il a aussi été observé chez 9 % (4/45) des patients ayant reçu du bicarbonate par voie intraveineuse à titre préventif et chez 25 % (2/8) des patients qui n'en avaient pas reçu ($p = 0.22$). Les stratégies de traitement comprenaient le rasburicase, le bicarbonate par voie intraveineuse, le furosémide et la thérapie de remplacement rénal.

Conclusions : Dans cet examen rétrospectif des dossiers, l'usage du rasburicase était plus fréquent pour les patients présentant un risque élevé, tandis que celui d'autres agents était similaire entre les groupes à risque. Ce schéma d'utilisation n'est pas conforme aux lignes directrices, qui

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recommandent que tous les patients présentant un risque élevé reçoivent du rasburicase. Aucune différence n'est apparue dans l'incidence du SLT parmi les patients ayant reçu du rasburicase ou du bicarbonate par voie intraveineuse à titre préventif et parmi ceux qui n'en avaient pas reçu. Davantage d'études prospectives sont nécessaires pour mieux connaitre la gestion des patients à haut risque ou ceux qui présentent des risques moyens de SLT, mais qui ont des malignités.

Mots clés : syndrome de lyse tumorale, rasburicase, bicarbonate, allopurinol

INTRODUCTION

Tumour lysis syndrome (TLS) is a medical emergency in which massive lysis of malignant cells upon exposure to cytotoxic therapy leads to metabolic derangements and organ dysfunction, including renal failure, seizures, and cardiac arrhythmias.[1] Acute lymphoblastic leukemia, acute myeloid leukemia, and aggressive non-Hodgkin lymphoma pose the greatest risk of TLS; however, other cancers with specific tumour-related factors (such as high sensitivity to cytotoxic therapy, high tumour burden, or high rate of proliferation) are also susceptible.[1,2] TLS may also occur spontaneously in the absence of cytotoxic therapy, but is more commonly induced by initial exposure to a cytotoxic agent such as hydroxyurea, steroid, or definitive chemotherapy.[3]

TLS is classified as either laboratory or clinical. Laboratory TLS is defined as 2 or more of the following within 3 days before or 7 days after exposure to cytotoxic therapy: uric acid ≥ 476 µmol/L or 25% increase from baseline, potassium ≥ 6.0 mmol/L or 25% increase from baseline, phosphate ≥ 1.45 mmol/L or 25% increase from baseline, or calcium ≤ 1.75 mmol/L or 25% decrease from baseline. Clinical TLS is defined as the occurrence of laboratory TLS plus 1 of the following: creatinine ≥ 1.5 times the institutional upper limit of normal, seizure, or cardiac arrhythmia/sudden death.[1]

A risk classification system, which stratifies patients as having low, intermediate, or high risk of TLS according to their type or stage of cancer, white blood cell count, and serum lactate dehydrogenase at time of presentation, is used to guide preventive therapy.[3] Prevention of TLS involves maintenance of adequate hydration and administration of medications to decrease serum uric acid, with the intention of preventing renal failure. Guidelines recommend that low-risk patients be actively monitored with careful attention to fluid status, and that intermediate-risk patients receive initial management with IV fluids and allopurinol to decrease production of uric acid, starting 1 to 2 days before definitive chemotherapy and continuing for up to 7 days afterward.[2,4] Rasburicase, a recombinant urate-oxidase enzyme that catalyzes the metabolism of poorly soluble uric acid to the more-soluble allantoin, is recommended for intermediate-risk patients if hyperuricemia develops despite prophylaxis with allopurinol.[2,4] High-risk patients should receive initial management with IV fluids and rasburicase.[2,4]

Treatment of established TLS involves interventions to target each laboratory abnormality, as dictated by its severity. Treatment may include IV administration of calcium to replenish serum calcium and to prevent arrhythmia, IV administration of insulin or sodium bicarbonate to induce intracellular potassium shift, administration of rasburicase to decrease serum uric acid, and administration of phosphate binders to decrease serum phosphate. In severe cases that have not responded to initial interventions, renal replacement therapy (RRT) may be required.[1] Electrocardiogram findings, urine output, and electrolytes should be assessed every 4 to 6 h, and admission to an intensive care unit (ICU) may be required for patients with no response to initial interventions.[1,2] The authors' institutions (described below) do not have a standardized approach to risk stratification for patients who present with malignancy and with intermediate or high risk of TLS, because there are no high-quality studies to inform such guidelines. As a result, there is likely variability in the approach to TLS prevention across these institutions.

The primary objective of this study was to characterize utilization of preventive strategies for patients with newly diagnosed hematologic malignancies who are at intermediate or high risk of TLS through comprehensive description of current practice (as one of our quality improvement initiatives). Secondary objectives were to determine TLS incidence, to compare use of preventive strategies among intermediate- and high-risk patients, and to describe TLS treatment strategies.

METHODS

Study Design

This multisite, retrospective chart review of patients admitted to Princess Margaret Cancer Centre (PM) and/or the affiliated ICU at Mount Sinai Hospital (MSH) in Toronto, Ontario, Canada, was an initial phase of the organizations' oncology quality improvement initiatives. Electronic medical records were reviewed alphabetically by last name to identify eligible patients admitted to either institution within the 1-year study period of October 1, 2015, to September 30, 2016. On the basis of historical admission

information for patients with hematologic malignancy at risk of TLS, we estimated that a 1-year time frame would provide an adequate sample size to thoroughly describe current practice.

This study was approved by the research ethics boards at PM and MSH, both of which waived the need for informed consent. The research was conducted in accordance with the Helsinki Declaration. A data transfer agreement was completed to permit transfer of information between the institutions.

Study Participants

Potential participants were identified using International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes for malignancies of interest or for TLS (Table 1). Patients were considered eligible if the reason for admission to the ICU at MSH or to PM was treatment of a newly diagnosed malignancy or treatment of suspected TLS. The TLS risk stratification criteria previously defined by an international expert panel were then applied to stratify patients as having low, intermediate, or high risk for TLS according to the type of malignancy, serum white blood cell count, and serum lactate dehydrogenase at the time of presentation (Table 2).[3,5] Patients were excluded from this study if they had low risk for TLS or if the reason for admission was management of a recurrent malignancy. We excluded low-risk patients because it was likely that use of preventive strategies in this group would be too infrequent for adequate characterization given that monitoring is the recommended management strategy for these patients.[2,4] We excluded patients with recurrent malignancy because we suspected that the risk of TLS among those experiencing relapse or refractory malignancy might have been affected by confounding factors, including the TLS preventive strategies employed during previous admissions.

Table 1. Codes from the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) Used to Identify Potential Participants

Condition	ICD-10 code
Acute myeloblastic leukemia	C92.0
Acute promyelocytic leukemia	C92.4
Acute myelomonocytic leukemia	C92.5
Acute myeloid leukemia with 11q23-abnormality	C92.6
Acute myeloid leukemia with multilineage dysplasia	C92.8
Acute monoblastic/monocytic leukemia	C93.0
Acute megakaryoblastic leukemia	C94.2
Acute lymphoblastic leukemia	C91.0
Diffuse large B-cell lymphoma	C83.3
Lymphoblastic (diffuse) lymphoma	C83.5
Mediastinal (thymic) large B-cell lymphoma	C85.2
Burkitt lymphoma	C83.7
Mature B-cell leukemia Burkitt-type	C91.8
Tumour lysis syndrome	E88.3

Definitions

We defined laboratory TLS as 2 or more of the following at any point within the data collection period: uric acid ≥ 476 μmol/L, potassium ≥ 6.0 mmol/L, phosphate ≥ 1.45 mmol/L, or calcium ≤ 1.75 mmol/L.[1] We did not account for changes from baseline, because baseline values could not be obtained for all patients. TLS was defined as spontaneous if the patient had not been exposed to any cytotoxic therapies (such as chemotherapy, steroids, or hydroxyurea) immediately before admission.

We defined clinical TLS as the presence of laboratory TLS plus 1 of the following: renal failure (defined as serum creatinine ≥ 1.5 times the institutional upper limit of normal), seizure, or

Table 2. Hematologic Malignancies of Interest and Associated Characteristics Used as Inclusion Criteria[3,5]

Malignancy	WBC/mL		LDH*
Intermediate risk			
Acute lymphoblastic leukemia	< 100 000	AND	< 2× ULN
Acute myeloid leukemia	25 000 to 100 000		
	< 25 000	AND	≥ 2× ULN
Burkitt lymphoma (early stage)			< 2× ULN
Diffuse large B-cell lymphoma			Above ULN
Lymphoblastic lymphoma (stage 1/2)			< 2× ULN
High risk			
Acute lymphoblastic leukemia	≥ 100 000	AND/OR	≥ 2× ULN
Acute myeloid leukemia	≥ 100 000		
Burkitt lymphoma (early stage)			≥ 2× ULN
Burkitt lymphoma (stage 3/4)	No specific criteria (all cases considered high risk)		
Burkitt leukemia	No specific criteria (all cases considered high risk)		
Diffuse large B-cell lymphoma			≥ 2× ULN
Lymphoblastic lymphoma (stage 1/2)			≥ 2× ULN
Lymphoblastic lymphoma (stage 3/4)	No specific criteria (all cases considered high risk)		

LDH = lactate dehydrogenase, ULN = upper limit of normal, WBC = white blood cell.
*Upper limit of normal for serum LDH was 220 units/L.

cardiac arrhythmia.[1] We did not include death as a marker for clinical TLS because death could not be definitively attributed to TLS alone in the context of a retrospective study. Clinical outcome data were obtained from clinical notes and discharge summaries.

Study Outcomes

The primary outcome was a description of current utilization of TLS preventive strategies, as indicated by the proportion of intermediate- and high-risk patients who received specific preventive strategies during admission, namely allopurinol, rasburicase, IV fluids (with or without sodium bicarbonate), and furosemide. The difference between the 2 risk groups in the proportions of patients who received each intervention was a secondary outcome. The 2 additional secondary outcomes were determination of TLS incidence and description of treatment strategies employed for patients who presented with TLS and for those in whom TLS developed during the admission.

Data Collection

For patients who received chemotherapy within 7 days of admission, data were collected from the day of admission up to 7 days after initiation of chemotherapy. For patients who did not receive chemotherapy within 7 days of admission, data were collected for the first 7 days of the hospital stay. For patients who were transferred between PM and MSH, data were collected from both institutions if the transfer occurred within the data collection window. Data were collected by trained investigators at both sites and were audited by a single investigator (S.M.).

Statistical Analysis

Data were analyzed using the χ^2 and Fisher exact tests for categorical variables. All of the tests were 2-sided, and the results were considered statistically significant if p was less than 0.05. Statistical analyses were performed using Stata software, version 11.2 (StataCorp LLC, College Station, Texas).

RESULTS

Study Population

Of 313 patients screened, 58 met the inclusion criteria (Figure 1). Twenty-nine patients (50%) were deemed to be at intermediate risk of TLS and 29 (50%) were deemed to be high

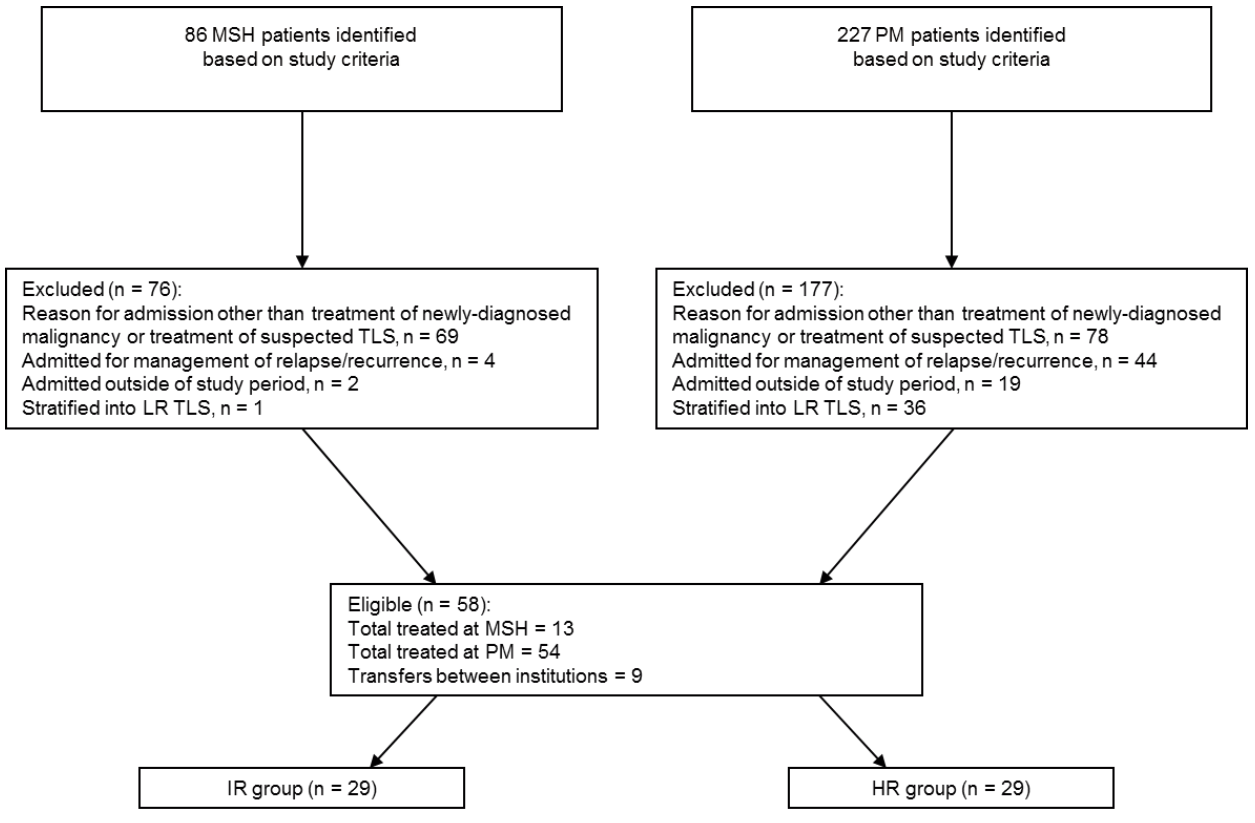

Figure 1. Patient flow diagram. Two patients met the study inclusion criteria both at the time of their admission to Princess Margaret Cancer Centre (PM) and at the time of their transfer from PM to the intensive care unit of Mount Sinai Hospital (MSH). LR = low risk, IR = intermediate risk, HR = high risk, TLS = tumour lysis syndrome.

risk. Two patients met the study inclusion criteria both at the time of their admission to PM and at the time of their transfer to MSH from PM; for each of these patients, the data for the 2 admissions were merged. The study groups were not significantly different at baseline (Table 3). Most of the patients (76% [44/58]) presented with either acute lymphoblastic leukemia or acute myeloid leukemia, and most (91% [53/58]) received chemotherapy within 7 days of admission.

Table 3. Demographic and Baseline Clinical Characteristics

Characteristic	Group; No. (%) of Patients*			*p* Value
	All (*n* = 58)	IR Group (*n* = 29)	HR Group (*n* = 29)	
Sex, male	34 (59)	17 (59)	17 (59)	> 0.99
Age (years) (median and range)	58 (25–82)	63 (25–82)	54 (25–78)	0.23
Weight (kg) (median and range)	77 (43–80)	81 (45–85)	69 (43–145)	0.026
Institution				0.29
Princess Margaret Cancer Centre	54 (93)	28 (97)	26 (90)	
Mount Sinai Hospital ICU	13 (22)	4 (14)	9 (31)	
Both institutions (by transfer)	9 (16)	3 (10)	6 (21)	
Reason for admission				0.49
Induction chemotherapy	56 (97)	29 (100)	27 (93)	
Treatment of suspected TLS	2 (3)	0 (0)	2 (7)	
Transfer from community hospital†	17 (29)	6 (21)	11 (38)	0.16
Presented with TLS‡				
Induced	2 (3)	0 (0)	2 (7)	
Spontaneous	2 (3)	0 (0)	2 (7)	
Type of malignancy				0.30
Acute myeloid leukemia	27 (47)	13 (45)	14 (48)	
Acute lymphoblastic leukemia	17 (29)	9 (31)	8 (28)	
Acute promyelocytic leukemia (APL)	6 (10)	5 (17)	1 (3)	
Diffuse large B-cell lymphoma	7 (12)	2 (7)	5 (17)	
Burkitt lymphoma	1 (2)	0 (0)	1 (3)	
Cytotoxic therapy before admission				
Any cytotoxic agent	26 (45)	14 (48)	12 (41)	
Hydroxyurea	15 (26)	8 (28)	7 (24)	0.78
Steroid	13 (22)	8 (28)	5 (17)	0.37
ATRA	2 (3)	1 (3)	1 (3)	
Imatinib	1 (2)	1 (3)	0 (0)	
Preventive therapy before admission				
Allopurinol	26 (45)	15 (52)	11 (38)	0.31
Rasburicase	1 (2)	0 (0)	1 (3)	> 0.99
Chemotherapy initiated				0.42
≤ 7 days from admission	53 (91)	28 (97)	25 (86)	
> 7 days from admission	3 (5)	1 (3)	2 (7)	
No chemotherapy	2 (3)	0 (0)	2 (7)	
Chemotherapy regimen: leukemia				
Daunorubicin/cytarabine (7 + 3)	17 (29)	6 (21)	11 (38)	
Dana Farber	16 (28)	9 (31)	7 (24)	
FLAG+IDA	6 (10)	5 (17)	1 (3)	
Low-dose cytarabine	4 (7)	1 (3)	3 (10)	
High-risk APL (arsenic + ATRA + idarubicin)	2 (3)	2 (7)	0 (0)	
Low-risk APL (arsenic + ATRA)	2 (3)	2 (7)	0 (0)	
ATRA	1 (2)	1 (3)	0 (0)	
Chemotherapy regimen: lymphoma				
R-CHOP	4 (7)	1 (3)	3 (10)	
High-dose methotrexate + cytarabine	2 (3)	1 (3)	1 (3)	
Etoposide	1 (2)	1 (3)	0 (0)	
Other	1 (2)	0 (0)	1 (3)	

ATRA = all-trans retinoic acid, FLAG+IDA = fludarabine–cytarabine–filgrastim–idarubicin, HR = high risk, ICU = intensive care unit, IR = intermediate risk, R-CHOP = prednisone–doxorubicin–vincristine–cyclophosphamide–rituximab, TLS = tumour lysis syndrome.
*Except where indicated otherwise.
†Of the 17 patients who were transferred from a community hospital, 13 were admitted to Princess Margaret Cancer Centre and 4 were admitted directly to the ICU at Mount Sinai Hospital.
‡TLS was defined as induced if the patient had been exposed to any cytotoxic therapy (such as steroids or hydroxyurea) directly before admission, and spontaneous in the absence of such exposure.

Use of Preventive Strategies

Use of certain preventive strategies did not differ between the intermediate- and high-risk groups (Table 4): allopurinol, 90% versus 92% ($p > 0.99$); IV fluids, 83% with bicarbonate and 14% without bicarbonate versus 84% with bicarbonate and 16% without bicarbonate ($p > 0.99$); and furosemide, 14% versus 12% ($p > 0.99$). Use of preventive rasburicase was significantly higher in the high-risk group (3% versus 36%; $p = 0.003$). For all patients who received allopurinol for TLS prevention, the dosage was 300 mg once daily. For all patients who received rasburicase for TLS prevention, the dose was 4.5 mg. Of the 10 patients who received preventive rasburicase, 4 had serum uric acid at or above 476 µmol/L.

Incidence of TLS

All Participants

There were 10 cases of TLS in total: for 6 patients, TLS developed during the hospital stay, and for 4 patients, TLS was present at the time of admission. Among the 54 patients who did not have TLS at the time of presentation, 29 were at intermediate risk and 25 at high risk. Among those at intermediate risk, TLS occurred in 4 patients and did not occur in the remaining 25 patients; among those at high risk, TLS occurred in 2 patients and did not occur in the remaining 23 patients (Figure 2). Of the 4 intermediate-risk patients in whom laboratory TLS occurred, 3 also experienced clinical TLS. Of the 2 high-risk patients in whom laboratory TLS occurred, both also experienced clinical TLS. In 1 high-risk patient, laboratory TLS developed 3 days before initiation of definitive chemotherapy; for the remaining 5 patients with laboratory TLS, it occurred after chemotherapy initiation. Laboratory abnormalities observed in the 10 patients with TLS are shown in Table 5.

All 4 patients who presented with TLS at the time of admission were at high risk and presented with clinical TLS. Three of these patients had acute myeloid leukemia, and 1 had diffuse large B-cell lymphoma.

Abnormal laboratory findings were more common in high-risk than in intermediate-risk patients. Several patients had an abnormal result for only 1 laboratory parameter and thus did not satisfy the criteria for laboratory TLS (Table 6).

Table 4. Utilization of Preventive Strategies According to Risk of Tumour Lysis Syndrome

Preventive Strategy	Risk Level; No. (%) of Patients		*p* Value
	Intermediate Risk (*n* = 29)	High Risk (*n* = 25)	
Allopurinol	26 (90)	23 (92)	> 0.99
Rasburicase	1 (3)	9 (36)	0.003
IV fluids			> 0.99
With bicarbonate	24 (83)	21 (84)	
Without bicarbonate	4 (14)	4 (16)	
Furosemide	4 (14)	3 (12)	> 0.99

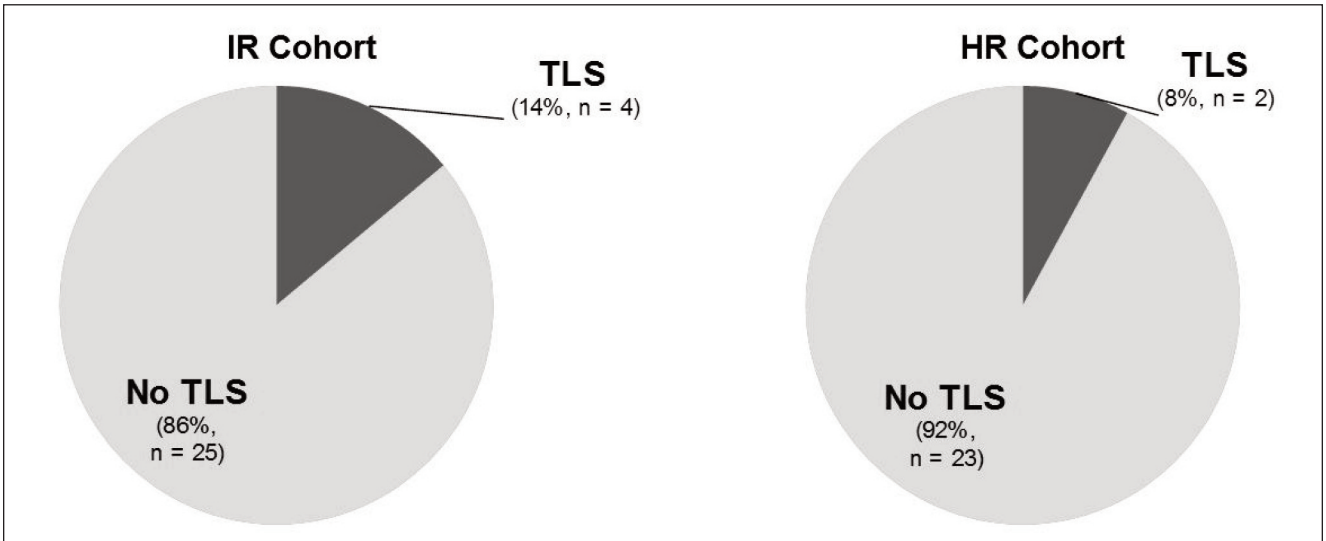

Figure 2. Occurrence of tumour lysis syndrome (TLS) among patients who did not present with TLS.
IR = intermediate risk, HR = high risk.

Table 5. Incidence of Abnormal Laboratory Values in Patients with TLS

Abnormality	Occurrence of TLS; No. (%) of Patients	
	Patient Presented with TLS (*n* = 4)	TLS Developed in Hospital (*n* = 6)
Uric acid ≥ 476 µmol/L	4 (100)	4 (67)
Potassium ≥ 6 mmol/L	1 (25)	2 (33)
Phosphate ≥ 1.45 mmol/L	4 (100)	6 (100)
Calcium ≤ 1.75 mmol/L	1 (25)	4 (67)

TLS = tumour lysis syndrome.

Table 6. Incidence of Abnormal Laboratory Values According to Risk Level

Abnormality	Risk Level; No. (%) of Patients	
	Intermediate Risk (*n* = 29)	High Risk (*n* = 29)
Uric acid ≥ 476 µmol/L	4 (14)	9 (31)
Potassium ≥ 6 mmol/L	1 (3)	2 (7)
Phosphate ≥ 1.45 mmol/L	21 (72)	24 (83)
Calcium ≤ 1.75 mmol/L	3 (10)	4 (14)

Table 7. Characteristics of Patients with Clinical Tumour Lysis Syndrome (CTLS) Who Received or Did Not Receive Renal Replacement Therapy (RRT)*

Patient Designation and Categorization	Electrolyte Abnormalities†	Decreased Urine Output‡	Serum Creatinine ≥ 1.5 ULN§
CTLS developed during admission			
RRT initiated			
1-010	Yes (K 6.8 mmol/L)	–	No
1-051	Yes (K 6.8 mmol/L)	–	Yes
1-057	Yes	Sudden decrease	Yes
RRT not initiated			
1-011	Yes	–	Yes
1-040	Yes	–	Yes
Patient presented with CTLS**			
1-021	Yes	–	Yes
1-038	Yes (K 6.6 mmol/L)	–	Yes
1-052	Yes	–	Yes
1-058	Yes	–	Yes

K = potassium, ULN = upper limit of normal.
*Characteristics shown in this table (electrolyte abnormalities, decrease in urine output, serum creatinine level) were considered consistent with clinical tumour lysis syndrome only if they occurred simultaneously.
†Elevated serum potassium, elevated serum uric acid, elevated serum phosphate, or decreased serum calcium. If serum potassium was elevated, the value is specifically indicated.
‡Urine output was recorded for patients admitted to the intensive care unit at Mount Sinai Hospital, but not for those admitted to Princess Margaret Cancer Centre. Therefore, this variable could not be reported for some patients.
§Upper limit of normal for serum creatinine was defined as 80 µmol/L for women and 105 µmol/L for men.
**None of the patients who presented with tumour lysis syndrome received renal replacement therapy.

Each of the 5 patients in whom clinical TLS developed during admission had documented acute kidney injury, and 3 of these received RRT. Each of these 5 patients had received chemotherapy within 7 days of admission. One of these 5 patients had a documented cardiac arrhythmia (serum potassium level was normal throughout the admission). All 4 patients in whom clinical TLS was present at the time of admission had documented acute kidney injury, although none received RRT. One of these patients had a documented cardiac arrhythmia (serum potassium on admission was 6.6 mmol/L). Characteristics of patients with clinical TLS who did and did not receive RRT are shown in Table 7.

Patients Who Received Preventive Rasburicase and/or IV Sodium Bicarbonate

Of the 10 patients who received preventive rasburicase, 1 (10%) experienced clinical TLS. Of the 44 patients who did not receive preventive rasburicase, 5 (11%) experienced laboratory TLS and 4 (9%) also experienced clinical TLS. There was no statistically significant difference in incidence of TLS between those who did and did not receive preventive rasburicase (Table 8).

Of the 45 patients who received preventive IV sodium bicarbonate, 4 (8%) experienced laboratory TLS, and 3 (6%) also

experienced clinical TLS. Of the 8 patients who did not receive preventive IV sodium bicarbonate, 2 (25%) experienced clinical TLS. There was no statistically significant difference in incidence of TLS between those who did and did not receive preventive IV sodium bicarbonate (Table 8).

Treatment Strategies

All 10 patients with TLS (either present at time of admission [n = 4] or occurring during the hospital stay [n = 6]) required interventions for treatment of TLS.

Of the 4 patients who presented with TLS, all had serum uric acid at or above 476 µmol/L, and all received rasburicase. Two of these patients received a single dose of rasburicase, and the other 2 patients received 2 doses. Of these latter 2 patients (who received 2 doses), only 1 had serum uric acid at or above 476 µmol/L after the first dose. All 4 patients who presented with TLS received IV fluids containing sodium bicarbonate. RRT was not initiated for any of these patients (Figure 3).

Of the 6 patients in whom TLS developed during admisson, 4 had serum uric acid at or above 476 µmol/L, yet only 1 received rasburicase. Four of these 6 patients received IV fluids containing sodium bicarbonate, whereas the remaining 2 received IV fluids without sodium bicarbonate. RRT was initiated for 3 of these 6 patients.

Admission to ICU

Fifty-four of the 58 patients in this study were admitted directly to PM, and 9 of these (3 at intermediate risk and 6 at high risk) were later transferred to MSH for ICU care. In 5 of the transferred patients, the development of TLS occurred directly before transfer (4 cases of induced TLS and 1 case of spontaneous TLS). Three of the transferred patients died in the ICU; all had experienced induced TLS on the day of transfer. RRT had been initiated for 2 of these patients but not for the third patient, despite severe electrolyte abnormalities.

The remaining 4 patients were admitted directly to the ICU at MSH (3 at high risk, 1 at intermediate risk). Chemotherapy was not initiated for 2 of these patients, and both died shortly after admission. Chemotherapy was initiated for the other 2 patients. One of these patients (who was at high risk) had acute myeloid leukemia and died on the day of chemotherapy initiation; this patient had not experienced TLS at any point. The other patient (who was at intermediate risk) also had acute myeloid leukemia, experienced TLS after initiation of chemotherapy, and required RRT but did not die.

DISCUSSION

In this multicentre review of TLS preventive strategies, we observed variability in the approach to TLS prevention between intermediate- and high-risk patients. Preventive rasburicase was used more frequently for high-risk patients, although not all patients in this risk category received the intervention. Use of allopurinol, IV fluids (with or without bicarbonate), and furosemide was similar between the intermediate- and high-risk groups.

Urinary Alkalinization for TLS Prevention

In this study, 83% of patients received IV fluids containing sodium bicarbonate for TLS prevention, a practice that clinical guidelines recommend against.[2,4] Urinary alkalinization increases uric acid solubility, decreasing precipitation of uric acid crystals in the renal tubules and preventing any obstruction that might otherwise ensue.[6] However, alkalinization does not prevent deposition of calcium phosphate crystals; rather, the solubility of calcium phosphate decreases with increasing pH, which increases the risk of obstruction and acute kidney injury.[7] Additionally,

Table 8. Incidence of Tumour Lysis Syndrome in Relation to Receipt of Rasburicase and/or IV Fluids Containing Sodium Bicarbonate for Prevention*

	Rasburicase†		Sodium Bicarbonate‡	
Cohort	**Yes (n = 10)**	**No (n = 44)**	**Yes (n = 45)**	**No (n = 8)**
Intermediate risk (n = 29)				
LTLS	0 (0)	4 (9)	2 (4)	2 (25)
CTLS	0 (0)	3 (7)	1 (2)	2 (25)
High risk (n = 25)				
LTLS	1 (10)	1 (2)	2 (4)	0 (0)
CTLS	1 (10)	1 (2)	2 (4)	0 (0)

CTLS = clinical tumour lysis syndrome, LTLS = laboratory tumour lysis syndrome.
*Data presented in this table are for the 54 patients who did not have tumour lysis syndrome at the time of presentation; data for the 4 patients who had this condition on presentation are excluded. Data are shown as number (%) of patients, based on n value at the top of each column.
†There was no significant difference in the occurrence of TLS among patients who did and did not receive preventive rasburicase, for both risk categories combined ($p > 0.99$).
‡Sodium bicarbonate data are shown for a total of 53 patients (1 patient did not receive any IV fluids). There was no significant difference in the occurrence of TLS among patients who did and did not receive preventive sodium bicarbonate, for both risk categories combined ($p = 0.22$).

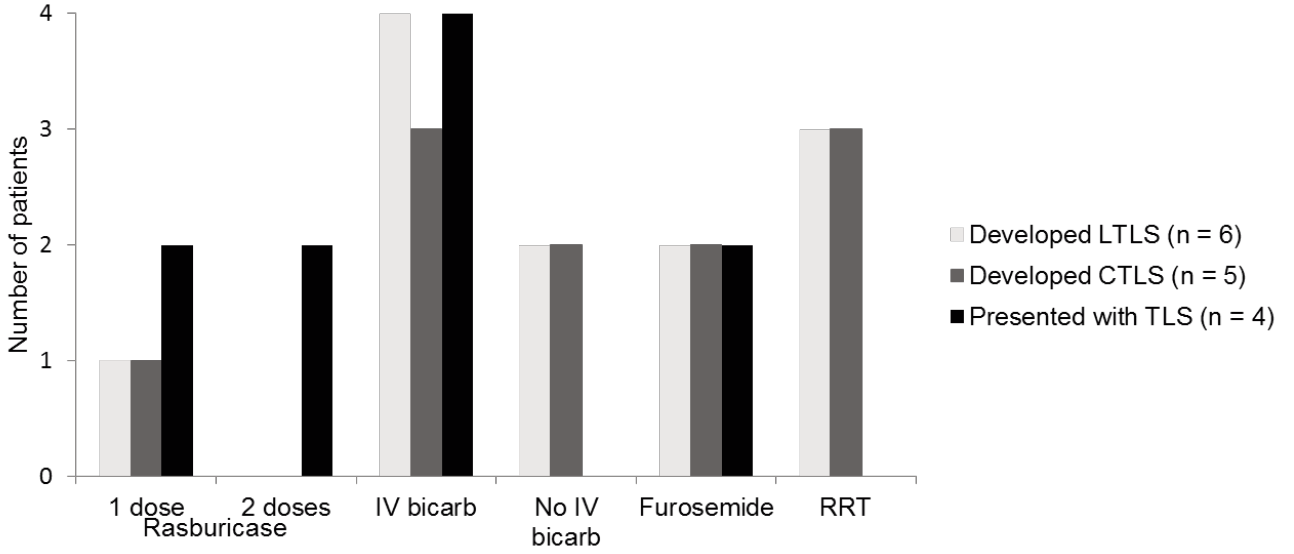

Figure 3. Utilization of treatment strategies for established laboratory tumour lysis syndrome (LTLS) or clinical tumour lysis syndrome (CTLS). Bicarb = sodium bicarbonate, RRT = renal replacement therapy.

alkalinization does not increase the solubility of the uric acid precursors xanthine and hypoxanthine. Because the levels of these precursors are elevated in patients receiving allopurinol, this represents a potential additional cause of acute kidney injury.[6] Administration of sodium bicarbonate has also been shown to increase carbon dioxide production and to worsen respiratory distress in susceptible patients, which may warrant ICU admission.[8-10] Efficacy of the intervention in preventing acute nephropathy has not been demonstrated, and the evidence is limited to a single animal study in which urinary alkalinization was not effective in preventing intrarenal deposition of urate.[11] Despite the lack of evidence for efficacy and numerous concerns about potential harm, administration of sodium bicarbonate is a strategy that continues to be employed at our institutions. We did not observe a statistically significant difference in incidence of TLS between patients who did and did not receive preventive IV sodium bicarbonate. Since 2017, the practice at our institutions has been to omit bicarbonate from IV fluids.

Rasburicase for TLS Prevention

In this study, 14% of intermediate-risk and 28% of high-risk patients had elevated serum uric acid within the data collection window, and 3% of intermediate-risk and 36% of high-risk patients received preventive rasburicase. It is likely that more of the high-risk patients received preventive rasburicase because they presented with more extreme metabolic derangements. Notably, the pattern of rasburicase use that we observed is inconsistent with clinical guidelines, which currently recommend that all high-risk patients receive initial management with rasburicase for TLS prevention.[2,4]

We did not observe a statistically significant difference in incidence of TLS between patients who did and did not receive preventive rasburicase. The efficacy of rasburicase in reducing serum uric acid in adults at risk for TLS has been well characterized.[12-14] Studies have investigated the efficacy of fixed- and weight-based dosing in reducing serum uric acid, although whether these dosing regimens produce favourable clinical outcomes (such as reduction in incidence of acute kidney injury and need for RRT) has not been determined.[15-19] The manufacturer of rasburicase recommends a daily dose of 0.20 mg/kg for up to 7 days for treatment and prophylaxis of hyperuricemia.[20] In one study, which compared rasburicase 0.15 mg/kg administered as a single dose followed by daily as-needed doses with a fixed regimen of 5 daily doses, administration of a single dose produced a sustained decrease in serum uric acid, and few patients who received the single dose required additional doses of rasburicase.[21] It is standard practice at the authors' institutions to administer 4.5 mg of rasburicase to patients at risk of TLS, so we are unable to comment on whether administration of a weight-based dose would decrease TLS incidence in our setting. The possibility of a specific population that would derive clinical benefit from use of a preventive weight-based dose of rasburicase remains to be elucidated.

Of the 10 patients in our study who received preventive rasburicase, only 4 had a serum uric acid at or above 476 µmol/L at the time of administration. In late 2019, the cost of a single 4.5-mg dose of rasburicase at one of the study institutions was approximately $410, and thus judicious prescribing is warranted. Studies investigating the efficacy of rasburicase in reducing serum uric acid generally include patients whose serum uric acid is

elevated at the time of presentation. As a result, it is unknown whether there is benefit in administering rasburicase to those with serum uric acid below this threshold. Furthermore, only 1 of the 4 patients who had laboratory TLS on admission and who also had elevated serum uric acid received rasburicase for treatment. Our institutions would benefit from reassessment of rasburicase prescribing practices to ensure that the medication is being used judiciously in the population most likely to derive benefit.

Additional Outcomes

In this study, TLS developed during admission for 14% of intermediate-risk and 8% of high-risk patients. It has been estimated that intermediate-risk patients have a 1%–5% chance of tumour lysis, whereas high-risk patients have a greater than 5% risk of tumour lysis.[3] We observed that high-risk patients were more likely than intermediate-risk patients to have a relevant laboratory abnormality, which might have prompted more aggressive management (for example, administration of a higher volume of IV fluids) to decrease the likelihood of TLS.

Strategies employed for the treatment of TLS were similar between those who presented with TLS and those in whom TLS developed during the admission, although a comparative analysis of treatment interventions was not performed because of the small sample size. Only 1 of the 2 patients who presented with TLS and who received 2 doses of rasburicase had persistence of serum uric acid above 476 µmol/L before administration of the second dose. Interestingly, 3 of the 6 patients in whom laboratory TLS developed during admission had serum uric acid above 476 µmol/L yet did not receive rasburicase; 2 of these patients also experienced clinical TLS (in the form of acute kidney injury). The decision to not administer rasburicase in these instances was likely multifactorial and influenced by the acuity of the patient's presentation, in combination with the decision to pursue other management strategies when possible (e.g., RRT in the ICU).

Strengths and Limitations

To our knowledge, this is the first study to investigate prescribing practices related to TLS prevention strategies in Canada and to associate these practices with clinical outcomes. We included patients from a malignant hematology service and an affiliated ICU in Toronto to reflect inter-institutional prescribing practices. We set specific, evidence-based criteria for inclusion, exclusion, and risk stratification in an effort to maintain uniformity of the study population.

We relied on ICD-10 codes to identify potential participants, under the assumption that patient charts had been accurately and thoroughly coded. The risk of selection bias because of the retrospective study design limits our ability to conclusively assess the impact of preventive strategies on clinical outcomes or to provide specific recommendations for practice.

Future Directions

Previous studies have demonstrated success in changing practice with interventions such as education and modification of standard order sets.[22] On the basis of our study findings, we recommended several changes to practice at our own institutions. Hydration with IV sodium bicarbonate should no longer be used for TLS prevention, given its uncertain benefit and potential harms, and our institutions have already discontinued this practice by removing this option from standard order sets. We are currently reviewing prescribing practices for rasburicase, because the pattern of use that we observed neither complies with clinical guidelines nor appears to be associated with a reduction in incidence of TLS. We are investigating strategies for optimization of rasburicase use, such as the use of alternative dosing regimens or the use of this drug in specific patient populations. In general, clinicians and patients would benefit from larger-scale research to better guide TLS risk stratification and management of case for patients with hematologic malignancy.

CONCLUSION

At the study institutions, almost all patients admitted with hematologic malignancy who were at intermediate or high risk for TLS received IV fluids and allopurinol to prevent TLS. Most patients received IV fluids containing sodium bicarbonate for this purpose, despite guidelines recommending against its use. Preventive rasburicase was more commonly used in patients at high risk, although use of this drug was not universal within this group despite the recommendations of clinical guidelines. Among all patients, there was no difference in TLS incidence between those who did and did not receive preventive IV sodium bicarbonate or rasburicase, although the numbers were small. Higher-quality evidence is needed to guide risk stratification and management for patients at intermediate and high risk of TLS.

References

1. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol.* 2004;127(1):3-11.
2. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* 2008;26(16):2767-78.
3. Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol.* 2010;149(4):578-86.
4. Jones GL, Will A, Jackson GH, Webb NJA, Rule S. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol.* 2015;169(5):661-71.
5. Executive Committee of the Medical Staff. *Tumour lysis syndrome (TLS) in adult patients.* Version 2. Houston (TX): University of Texas MD Anderson Cancer Center, Department of Clinical Effectiveness; 2018 [cited 2019 Nov 21]. Available from: https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-tumor-lysis-web-algorithm.pdf
6. Sood AR, Burry LD, Cheng DKF. Clarifying the role of rasburicase in tumor lysis syndrome. *Pharmacotherapy*. 2007;27(1):111-21.
7. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med.* 2011;364(19):1844-54.

8. Adrogué HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. *N Engl J Med.* 1989;320(20):1312-6.
9. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. *PLoS One.* 2013;8(6):e65283.
10. Adeva-Andany MM, Fernández-Fernández C, Mouriño-Bayolo D, Castro-Quintela E, Domínguez-Montero A. Sodium bicarbonate therapy in patients with metabolic acidosis. *Sci World J*. 2014;2014:Article 627673.
11. Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. *J Clin Invest.* 1977;59(5):786-93.
12. Cortes J, Moore JO, Maziarz RT, Wetzler M, Craig M, Matous J, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—results of a multicenter phase III study. *J Clin Oncol*. 2010;28(27):4207-13.
13. Pui CH, Jeha S, Irwin D, Camitta B. Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia*. 2001;15(10):1505-9.
14. Coiffier B, Mounier N, Bologna S, Fermé C, Tilly H, Sonet A, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Étude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol.* 2003;21(23):4402-6.
15. McDonnell AM, Lenz KL, Frei-Lahr DA, Hayslip J, Hall PD. Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. *Pharmacotherapy*. 2006;26(6):806-12.
16. Trifilio SM, Pi J, Zook J, Golf M, Coyle K, Greenberg D, et al. Effectiveness of a single 3-mg rasburicase dose for the management of hyperuricemia in patients with hematological malignancies. *Bone Marrow Transplant.* 2011; 46(6):800-5.
17. Reeves DJ, Bestul DJ. Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. *Pharmacotherapy*. 2008;28(6):685-90.
18. Campara M, Shord SS, Haaf CM. Single-dose rasburicase for tumour lysis syndrome in adults: weight-based approach. *J Clin Pharm Ther.* 2009; 34(2):207-13.
19. McBride A, Lathon SC, Boehmer L, Augustin KM, Butler SK, Westervelt P. Comparative evaluation of single fixed dosing and weight-based dosing of rasburicase for tumor lysis syndrome. *Pharmacotherapy*. 2013;33(3):295-303.
20. Fasturtec (rasburicase) [product monograph]. Laval (QC): Sanofi-Aventis Canada Ltd; 2016.
21. Vadhan-Raj S, Fayad LE, Fanale MA, Pro B, Rodriguez A, Hagemeister FB, et al. A randomized trial of a single-dose rasburicase versus five-daily doses in patients at risk for tumor lysis syndrome. *Ann Oncol*. 2012;23(6):1640-5.
22. Fan-Lun C, Chung C, Lee EHG, Pek E, Ramsden R, Ethier C, et al. Reducing unnecessary sedative-hypnotic use among hospitalised older adults. *BMJ Qual Saf*. 2019;28(12):1039-45.

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ORIGINAL RESEARCH

Recall of Pharmaceutical Pictograms by Older Adults

Régis Vaillancourt, Cindy N Giby, Bradley P Murphy, Annie Pouliot, and Anne Trinneer

ABSTRACT

Background: Low health literacy and high medication burden in the older adult population are contributing factors to the misunderstanding of medication instructions, leading to an increased risk of poor adherence and adverse events in this group of patients.

Objective: To evaluate the ability of older adults to recall the meaning of 13 pharmaceutical pictograms 4 weeks after receipt of feedback on pictogram meaning.

Methods: Older adults (aged 65 or older) were recruited from one community pharmacy in Canada. One-on-one structured interviews were conducted to assess the comprehensibility of 13 pharmaceutical pictograms from the International Pharmaceutical Federation's database of pictograms. Each participant was then told the meaning of each pictogram. Recall was assessed 4 weeks later.

Results: A total of 58 participants met the inclusion criteria and agreed to participate. The number of pictograms meeting the ISO threshold for comprehensibility of symbols increased from 10 at the initial comprehensibility assessment to 13 at the recall assessment. Analysis of demographic data showed no associations between initial comprehensibility of the pictograms and age, sex, education level, or number of medications taken.

Conclusions: The results of this study indicate that after being informed of the meaning of pharmaceutical pictograms, older adults were able to recall the pictogram meanings for at least 4 weeks.

Keywords: pharmaceutical pictograms, older adults, recall, and comprehensibility

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RÉSUMÉ

Contexte : Les faibles connaissances en matière de santé des personnes âgées et le lourd fardeau des médicaments qui pèse sur elles sont des facteurs qui contribuent à l'incompréhension des instructions relatives à l'administration des médicaments, ce qui entraîne un risque plus élevé de mauvaise adhésion au traitement et d'événements indésirables dans ce groupe de patients.

Objectif : Évaluer la capacité des adultes plus âgés à se souvenir du sens des 13 pictogrammes pharmaceutiques, quatre semaines après avoir été informés de leur sens.

Méthodes : Les adultes plus âgés (65 ans et au-delà) ont été recrutés dans une pharmacie communautaire du Canada. Des entrevues structurées en tête-à-tête ont été menées pour évaluer l'intelligibilité de 13 pictogrammes pharmaceutiques extraits de la base de données de la Fédération internationale pharmaceutique. Le sens de chaque pictogramme a ensuite été communiqué à chaque participant et, quatre semaines plus tard, leur capacité à s'en souvenir a été évaluée.

Résultats : Cinquante-huit participants répondaient au critère d'inclusion et ont accepté de participer à l'étude. Le nombre de pictogrammes répondant au seuil ISO d'intelligibilité des symboles est passé de 10 (au moment de l'évaluation d'intelligibilité initiale) à 13 (au moment de l'évaluation du rappel). L'analyse des données démographiques n'a indiqué aucune association entre l'intelligibilité initiale des pictogrammes et l'âge, le sexe, le niveau de formation ou le nombre de médicaments que prenaient ces personnes.

Conclusions : Les résultats de cette étude indiquent qu'après avoir été informés du sens des pictogrammes pharmaceutiques, les aînés étaient en mesure de s'en souvenir pendant au moins quatre semaines.

Mots clés : pictogrammes pharmaceutiques, aînés, rappel et intelligibilité

INTRODUCTION

Many older adults take numerous medications. Individuals 65 years of age and older account for approximately 15% of the Canadian population, yet they are responsible for nearly 40% of all spending on prescribed medications.[1] In 2012, nearly two-thirds of older Canadian adults using public drug programs had claims for 5 or more drug classes.[1] Older adults are also more likely than younger people to have limited health literacy.[2-6] Health literacy is important in the effective management of chronic disease because it affects the ability to understand the nature of one's medical condition[7] and the ability to perform self-care, especially among older adults.[8,9] This combination of lower health literacy and high prescription drug use likely contributes to the fact that older adults are at high risk for adverse drug events[10] and for misinterpreting medication instructions.[11,12] Misunderstanding of medication instructions may lead to poor adherence[13,14] and medication errors.[15] Cognitive aging further contributes to this process, which poses an additional risk for non-adherence and adverse events.[13] Therefore, it is important to develop tools to help older adults to understand the instructions for taking their medications. Although adherence with medication therapy is multifactorial,[16] improved comprehension may improve adherence and clinical outcomes, which will in turn reduce health care costs.[17,18]

Pharmacists generally provide counselling about prescription medications just once, when a prescription is initially filled,[19] even though some medications are taken for many months or virtually indefinitely. During these consultations, information is provided verbally and/or in written form. Medical information presented verbally may not be well retained.[20,21] In addition, much of this written material is not adapted to match the patient's education level, and the documentation can be long and complex,[15,22,23] which may be challenging, especially for older adults.[24] Nonetheless, numerous reviews have demonstrated that the communication of medication information by pharmacists can be very effective. Pharmacist-led educational interventions have improved adherence to medication in depression,[25] type 2 diabetes,[26] and chronic obstructive pulmonary disease,[27] and have improved clinical outcomes in patients with type 2 diabetes[28] and hypertension.[29] The association between medication adherence and health services utilization and cost is well established, with even moderate improvement in adherence being associated with reductions in utilization and cost.[17,18] Thus, finding effective interventions to improve adherence is worth the effort.

One step toward improving medication adherence is to improve patients' understanding of medication instructions. Implementation of pictograms depicting key counselling points during medication consultations may improve comprehension and retention of these key points. Pictograms, when added to patient information, represent an intervention that has been shown to improve patient comprehension of health information generally[30,31] and medication information more specifically.[32,33] Many studies of pharmaceutical pictograms have been conducted in various populations. Pharmaceutical pictograms have been tested for their ability to improve understanding and recall of medication instructions in individuals with low literacy,[31,34] those taking long-term medications,[32,35-56] older adults,[32,38] women,[39] and adults.[40,41] Results have been mixed. The variation in these results may be explained, at least in part, by whether the pictograms were first demonstrated to be comprehensible in the population of interest.[42]

We know from numerous published studies on the comprehensibility of pharmaceutical pictograms that at least a few pictograms in each trial will not be understood by participants and that the extent of pictogram comprehensibility depends greatly on the population in which they are tested.[42] Researchers have tested pharmaceutical pictograms for comprehensibility in individual ethnic, cultural, and language groups[43-48]; in older adults[49-51]; in patients with low literacy[52-56]; in children and youth[57,58]; and in adults.[59-63] A recent review of patient involvement in pictogram design indicated that studies using an iterative process of design and redesign based on patient feedback tend to produce pictograms that are well understood.[42]

The purpose of this study was to evaluate the ability of older adults to understand and recall the meaning of pharmaceutical pictograms used to convey key medication counselling points. Recall was measured after a 1-month (4-week) interval because this is a typical refill period for prescription medications. Recall was assessed because of the possibility that some pharmaceutical pictograms may not be recognizable, no matter how often they are redesigned. It may be possible, however, that older adults will remember the meaning of a pictogram after being informed of its meaning.

METHODS

Pictograms

The 13 pictograms used in this study were taken from the International Pharmaceutical Federation (FIP) database (https://www.fipfoundation.org/pictogram-project/using-pictograms/). They depict key counselling points related to indications, side effects, routes and frequencies of administration, and precautions. All of these pictograms were developed using a patient-centred approach, with participants drawn from the general population.[64] Thus, they were not initially developed specifically for use in older adults; however, they were subsequently tested in a sample of older adults[51] using the International Organization for Standardization (ISO) criteria for development of public information symbols.[65] According to the ISO 9186-1 standard,[65] in order to be considered comprehensible, the meaning of a pictogram must be correctly understood by at least 66.7% of participants. In the initial study with older adults, pictograms that were not well understood were modified by a graphic designer on the basis of participants' suggestions, when available, and were then retested.[51] Despite redesign, 47 pictograms (out of 76) remained poorly understood in this sample of older adults.[51] This result not only highlighted the importance of testing pictograms for comprehensibility among older adults, but also suggested the

importance of including a recall phase in the experimental design. The meaning of some pictograms may never be "guessable" by some populations, but if participants can recall the meaning after it has been provided, this suggests that the pictogram may be able to convey its intended meaning when paired with information about its meaning. For the current study, we chose 13 pictograms from the previous study with older adults,[51] representing medication instructions that we considered to be most useful for older adults. Notably, 10 of these 13 pictograms did not meet the 66.7% threshold when initially tested with older adults.[51]

Participants

Individuals aged 65 years or older who had prescriptions for at least 3 medications were recruited from a single community pharmacy in Ottawa, Ontario, Canada. Potential participants were excluded if they resided in an assisted-living facility, had self-declared functional impairment (e.g., blindness), or were taking a medication for cognitive impairment (e.g., dementia). Visual acuity was not assessed. However, it is likely that cognitive impairment would affect the results of any test of pictogram comprehensibility. Therefore, the Mini-Cog,[66] a 3-item test of cognitive abilities that is as sensitive and specific in testing for dementia as the Mini–Mental State Exam and the Cognitive Abilities Screening Instrument, was administered to all potential participants. A Mini-Cog score of less than 3 (out of 5) indicates impaired cognitive status.[66] Only participants with a score of 4 or 5 were included in the present study. To validate pictograms for use with older adults who have cognitive impairment, it would be necessary to select a sample consisting entirely of participants with cognitive impairment; however, this was not the purpose of the current study.

Potential participants who did not meet the inclusion criteria or who did not agree to participate continued to receive services as usual in the pharmacy.

Data Collection and Outcome Measures

Demographic data collected were sex, age, education level, language spoken at home, and number of long-term medications being taken.

The comprehensibility of the pictograms was determined by an assessment of transparency. The concept of transparency refers to how easily the meaning of a symbol can be guessed when the referent is not present.[67] Participants' responses on transparency testing were scored as correct or incorrect by 2 independent raters (B.P.M. and A.P.). Any disagreements among the raters were discussed with a third person, and a decision on scoring was reached by consensus.

Procedure

When a potentially eligible participant came to the pharmacy to fill a prescription, a pharmacist or pharmacy technician asked whether he or she was interested in participating in the study. A fully bilingual (English and French) pharmacy technician conducted one-on-one structured interviews with participants, both during the initial assessment and at follow-up. The ability to conduct these interviews in either English or French was important because almost 9% of the population of Ottawa and surrounding area speak only French,[68] and we did not wish to exclude such a large proportion of the population. During the initial assessment, the interviewer first administered the Mini-Cog test to screen for cognitive impairment, as described above. Only participants who passed the Mini-Cog test were asked to complete the remainder of the assessment.

The 13 pictograms, printed on 25-cm^2 cue cards, were shuffled before each session and presented sequentially. For each pictogram, the participant was asked what he or she thought the pictogram meant in the context of taking medication. The responses were transcribed verbatim by the interviewer. Immediately after presenting all 13 pictograms, the interviewer then informed the participant of the intended meaning of each pictogram. The demographic questionnaire was administered at the end of this interview.

Four weeks later, the participants were invited (via telephone call from a pharmacy technician) to complete the recall assessment. During the recall assessment, which was conducted in person in the pharmacy, the identical procedure was followed, with the technician presenting the pictograms and asking the participant what he or she thought each pictogram meant in the context of taking medication. No other assessments or questionnaires were administered at the recall assessment.

Approval for this study was obtained from the Research Ethics Board of the Children's Hospital of Eastern Ontario. All participants provided written consent to participate in the research process. Each participant received a $10 gift card redeemable at the pharmacy.

Analyses

All analyses were conducted with IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, New York). Categorical variables were analyzed using frequencies and percentages. Normally distributed continuous variables were summarized using means and standard deviations (SDs). McNemar tests were performed to compare the number of participants who correctly understood the meaning of each pictogram during transparency testing with the number who correctly recalled the meaning 4 weeks later. A repeated-measures analysis of variance (ANOVA) was conducted to determine whether there was a difference between participants' comprehension of all pictograms before and after being told the meanings. Subgroup analyses were conducted using χ^2 analyses with the Fisher exact test to identify differences in pictogram comprehensibility in relation to highest level of education completed (middle/high school versus college, university, or postgraduate), sex, Mini-Cog test score (4 versus 5), and number of long-term medications being taken (3 or 4 versus 5 or more). Similarly, one-way ANOVAs were conducted to test for differences in pictogram comprehensibility by age. Given the large number of subanalyses carried out (n = 65), the threshold p value for significance in these analyses was set at 0.05/65 or 0.0007.

RESULTS

Demographic Characteristics

A total of 58 participants met the inclusion criteria and agreed to participate. This sample size was considered adequate because the ISO standard[65] states that pictograms should be tested with a minimum sample of 50 participants. Of the 58 participants who met the inclusion criteria and agreed to participate, 30 were women, 25 were men, and sex was not reported for 3 participants (Table 1). The mean age of participants was 74.2 (SD 6.1), with 26 (45%) being 75 years or older. There was no age difference between men (mean 74.8, SD 7.0) and women (mean 74.2, SD 5.5) ($t(53) = 0.38$, $p = 0.71$). Of those who provided information about their level of education, 98% (52/53) had completed at least high school. The mean number of prescription medications being taken by participants was 4.9 (SD 6.1), with 28% of participants taking 6 or more prescription medications. All 58 participants completed both the initial interview (transparency assessment) and the recall assessment.

Pictogram Comprehensibility

Of the 13 pictograms tested in this study, 10 reached the ISO standard for comprehensibility, with at least 66.7% of participants understanding the meaning during the transparency assessment, that is, upon initial presentation before being told the intended meaning (Table 2). The pictograms for "confusion" (52%), "diarrhea" (57%), and "take in the morning" (48%) did not meet the ISO comprehensibility threshold (Table 2). These 3 pictograms were also among those that did not meet the threshold in the previous study with older adults.[51]

During the recall assessment, 4 weeks after participants were told the meaning of the pictograms, all 13 pictograms reached the ISO standard for comprehensibility. Statistically significant differences in the proportions of participants comprehending the pictograms between the transparency and recall assessments were observed for 9 pictograms: "tremors", "confusion", "dizzy when getting up", "nausea", "diarrhea", "shake well", "do not crush", "take in the morning", and "seek medical assistance" (Table 2).

As an additional test of whether comprehension of the pictograms was better at the recall assessment than at the transparency assessment, a repeated-measures ANOVA was conducted, comparing the total number of pictograms understood correctly by each participant at the recall assessment with the total number understood at the transparency assessment. The result was statistically significant (Wilks $\lambda = 0.38$, $F[1,57] = 93.41$, $p < 0.001$), with the average number of pictograms understood correctly being higher at the recall assessment (mean 12.6, SD 0.8), than at transparency assessment (mean 9.9, SD 2.3).

Table 1. Demographic Characteristics of Participants

Characteristic	No. (%) of Participants ($n = 58$)
Age group (years)	
≥ 65 and < 75	32 (55)
≥ 75 and < 85	20 (34)
≥ 85	6 (10)
Sex	
Male	25 (43)
Female	30 (52)
Unknown	3 (5)
No. of medications	
3	11 (19)
4	13 (22)
5	8 (14)
≥ 6	16 (28)
Unknown	10 (17)
Language	
English	26 (45)
French	27 (47)
Bilingual	3 (5)
Other	2 (3)
Highest level of education completed	
Middle school	1 (2)
High school	19 (33)
College	8 (14)
University	18 (31)
Postgraduate	7 (12)
Unknown	5 (9)
Mini-Cog test score[66] (out of 5)	
4	24 (41)
5	34 (59)

Association between Characteristics and Comprehensibility

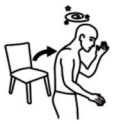
Our analyses indicated no statistically significant associations between pictogram comprehensibility and age, education level, sex, number of prescription medications, or Mini-Cog score (Table 3).

DISCUSSION

In this study, older adults could correctly recall the meaning of 13 pharmaceutical pictograms 4 weeks after initial assessment, even if they initially did not correctly understand the meaning of the pictogram. For 9 of the 13 pictograms tested—"tremors", "confusion", "dizzy when getting up", "nausea", "diarrhea", "shake well", "do not crush", "take in the morning", and "seek medical assistance"—more participants correctly stated the meaning at the recall assessment than at the initial presentation. In a previous study with older adult participants,[51] none of these pictograms met the ISO standard of 66.7% of participants being able to guess their meaning, but all participants in the current study met the standard at the recall assessment.

The 3 pictograms that met the ISO threshold for comprehensibility in the previous study with older adults study[51] ("take 1 tablet by mouth", "headache", and "do not mix with alcohol") also did so in the transparency assessment of the current study. The pictograms for "confusion", "diarrhea", and "take in the morning" did not meet the ISO threshold in either the previous study[51] or the transparency assessment of the current study. In

Table 2 (part 1 of 3). Comprehensibility and Recall Scores

Pictogram	No. (%) of Participants Who Correctly Identified Meaning (*n* = 58)		*p* Value*
	Transparency Assessment	Recall Assessment	
 Tremors	41 (71)	58 (100)	< 0.001
 Confusion	30 (52)	47 (81)	0.001
 Fatigue	51 (88)	56 (97)	0.13
 Dizzy when getting up	46 (79)	56 (97)	0.002
 Nausea	46 (79)	58 (100)	< 0.001

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*Tested by McNemar test for paired proportions. A *p* value less than 0.01 indicates that more participants understood the meaning of the pictogram at recall than at the transparency assessment.

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contrast to these similarities in results, 7 pictograms that were not understood by older adults previously[51] ("tremors", "fatigue", "nausea", "shake well", "do not crush", "seek medical assistance", and "dizzy when getting up") were guessed correctly by more than 66.7% of participants in the current study. There are some differences in the study samples that may explain why participants in the current study were able to understand the meaning of more of the pictograms. The mean age of participants in the current sample was 5 years younger than that of the sample in the previous study.[51] In addition, there was no screening for cognitive capacity in the previous study.[51] Thus, it is possible that the higher mean age in the previous study[51] was associated with age-related decline in cognitive capacity, which might have affected pictogram interpretability. Also, most participants in the previous study had fewer than 12 years of education, whereas the majority of the current sample had more than a high school education. It is likely that a sample with fewer years of education would also have lower health literacy. To understand the meaning of a pictogram within the context of taking medications, a person must draw upon health-related knowledge. Thus, it may be that participants in the current study had more knowledge upon which to draw when describing what they thought each pictogram meant in the context of taking medication.

The results of this study demonstrate the importance of counselling older adult patients to ensure they understand the meaning of the pictograms that accompany their

Table 2 (part 2 of 3). Comprehensibility and Recall Scores

Pictogram	No. (%) of Participants Who Correctly Identified Meaning (n = 58): Transparency Assessment	Recall Assessment	p Value*
 Diarrhea	33 (57)	55 (95)	< 0.001
 Shake well	44 (76)	58 (100)	< 0.001
 Do not crush	42 (72)	57 (98)	< 0.001
 Take in the morning	28 (48)	55 (95)	< 0.001
 Seek medical assistance	44 (76)	58 (100)	< 0.001

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*Tested by McNemar test for paired proportions. A p value less than 0.01 indicates that more participants understood the meaning of the pictogram at recall than at the transparency assessment.

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prescription medications. Del Re and others[31] conducted a literature review to evaluate the effectiveness of pictograms to improve patients' recall of medication safety instructions. They speculated that older adults have increased difficulty in recalling pictograms because of an unclear understanding of the information presented.[31] These authors proposed that special consideration be given to older adults and that indeed all patients should be counselled when pictograms are used in a health care setting. Their recommendation reflects current standards set by the FIP, which state that "graphic symbols for patient instruction should not be used alone but should always be combined with written instructions".[69] The importance of using pictograms together with verbal or written information has been documented in other studies[31,54,70] and has been considered from a theoretical standpoint in the dual coding theory proposed by Paivio.[71] This author stated that information is processed by verbal and nonverbal coding systems.[71] Furthermore, pictures or images trigger the activation of both systems to a greater extent than words alone, leading to improved recall of information.[71] By extension, the recruitment of multiple senses through the use of verbal and written instructions together with pictograms will likely lead to improved recall.

Table 2 (part 3 of 3). Comprehensibility and Recall Scores

Pictogram	No. (%) of Participants Who Correctly Identified Meaning (*n* = 58): Transparency Assessment	Recall Assessment	*p* Value*
 Take 1 tablet by mouth†	57 (98)	58 (100)	> 0.99
 Headache†	56 (97)	56 (97)	> 0.99
 Do not mix with alcohol†	57 (98)	58 (100)	> 0.99

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*Tested by McNemar test for paired proportions. A *p* value less than 0.01 indicates that more participants understood the meaning of the pictogram at recall than at the transparency assessment.
†Pictograms that met the ISO threshold of 66.7% of participants comprehending the meaning in a previous study with older adults.[51]

Table 3. Subanalysis of Initial Pictogram Comprehensibility in Relation to Demographic Characteristics

	Age†		Highest Education‡		Sex‡		No. of Medications‡		Mini-Cog Test Score‡	
Pictogram*	Test Value	*p* Value	Test Value	*p* Value	Test Value	*p* Value	Test Value	*p* Value	Test Value	*p* Value
Tremors	0.20	0.66	0.41	0.52	0.56	0.46	0.95	0.33	0.32	0.57
Confusion	0.99	0.33	0.29	0.59	0.02	0.88	0.34	0.56	0.72	0.40
Fatigue	0.08	0.77	2.41	0.12	0.44	0.51	2.01	0.16	0.82	0.37
Dizzy when getting up	1.70	0.20	0.21	0.65	0.46	0.50	0.00	1.00	0.46	0.50
Nausea	0.67	0.42	1.67	0.20	0.13	0.72	0.14	0.71	0.46	0.50
Diarrhea	1.25	0.27	1.76	0.19	0.79	0.37	4.15	0.04	0.03	0.85
Shake well	1.01	0.32	0.10	0.75	0.16	0.69	0.11	0.75	0.24	0.62
Do not crush	0.56	0.46	0.10	0.75	0.03	0.87	0.95	0.33	0.68	0.41
Take in the morning	0.82	0.37	1.05	0.31	0.20	0.66	0.34	0.56	0.05	0.83
Seek medical assistance	0.36	0.55	0.004	0.95	0.16	0.69	4.00	0.05	0.57	0.45
Take 1 tablet by mouth	0.02	0.90	1.68	0.20	0.85	0.36	1.02	0.31	0.72	0.40
Headache	0.56	0.46	1.26	0.26	2.49	0.12	2.09	0.15	0.06	0.80
Do not mix with alcohol	0.09	0.77	0.62	0.43	0.85	0.36	1.02	0.31	1.44	0.23

*See Table 2 for the pictograms.
†Tested by one-way analysis of variance.
‡Tested by χ^2 analysis with the Fisher exact test.

Limitations

Among the limitations of the current study is the fact that we did not assess participants' visual acuity. It is possible that some participants did not understand certain of the pictograms because of vision problems. In addition, we did not assess health literacy. Given that pictograms are often implemented to help people with low levels of health literacy to better understand their medication administration instructions, it will be important to investigate how well older adults with low health literacy understand these pictograms and recall their meanings. Potential participants with cognitive impairment were excluded from the current study. Thus, another limitation of the study is that the results can be generalized only to older adults without cognitive impairment.

Recommendations for Future Research

Given that the intended meaning of all 13 pictograms included in this study could be recalled by at least 66.7% of participants after 4 weeks, we recommend that future research in the development of pictograms with older adults should assess recall of pictogram meaning and not rely on transparency assessment alone. Given the low health literacy levels noted among older adults in other studies,[2-5] it may not always be possible for this age group to understand the meaning of pharmaceutical pictograms without explanation. They may, however, be able to recall pictogram meanings once they have been explained.

It would also be interesting to know whether use of these pictograms can increase adherence to medication regimens among older adults. Any future research on the effect of these pictograms on medication adherence among older adults should implement recently published guidelines for conducting effective research on medication adherence.[72]

Implications for Practice

Four weeks after being informed of the intended meanings of pictograms depicting medication instructions, older adults were able to recall the pictogram meanings. Thus, this set of pictograms may be used in practice with older adults to convey key counselling points, in combination with verbal and written instructions. As stated by FIP, "graphic symbols for patient instruction should not be used alone but should always be combined with written instructions".[69]

References

1. Proulx J, Hunt J. Drug use among seniors on public drug programs in Canada, 2012. *Healthc Q.* 2015;18(1):11-3.
2. *The full Canadian report of the international adult literacy and skills survey.* Ottawa (ON): Statistics Canada; 2005.
3. Kobayashi LC, Wardle J, Wolf MS, Von Wagner C. Aging and functional health literacy: a systematic review and meta-analysis. *J Gerontol Ser B Psychol Sci Soc Sci*. 2016;71(3):445-57.
4. Von Wagner C, Knight K, Steptoe A, Wardle J. Functional health literacy and health-promoting behaviour in a national sample of British adults. *J Epidemiol Community Health*. 2007;61(12):1086-90.
5. Paasche-Orlow MK, Parker RM, Gazmararian JA, Nielsen-Bohlman LT, Rudd RR. The prevalence of limited health literacy. *J Gen Intern Med.* 2005;20(2):175-84.
6. Zamora H, Clingerman EM. Health literacy among older adults: a systematic literature review. *J Gerontol Nurs.* 2011;37(10):41-51.
7. Du S, Zhou Y, Fu C, Wang Y, Du X, Xie R. Health literacy and health outcomes in hypertension: an integrative review. *Int J Nurs Sci*. 2018;5(3): 301-9.
8. Cho YI, Lee SYD, Arozullah AM, Crittenden KS. Effects of health literacy on health status and health service utilization amongst the elderly. *Soc Sci Med.* 2008;66(8):1809-16.
9. Hanchate AD, Ash AS, Gazmararian JA, Wolf MS, Paasche-Orlow MK. The Demographic Assessment for Health Literacy (DAHL): a new tool for estimating associations between health literacy and outcomes in national surveys. *J Gen Intern Med.* 2008;23(10):1561-6.
10. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol.* 2017;73(6):759-70.
11. Davis TC, Wolf MS, Bass PF 3rd, Thompson JA, Tilson HH, Neuberger M, et al. Literacy and misunderstanding prescription drug labels. *Ann Intern Med*. 2006;145(12):887-94.
12. Maher RL Jr, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf.* 2014;13(1):57-65.
13. Campbell NL, Boustani MA, Skopelja EN, Gao S, Unverzagt FW, Murray MD. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother.* 2012; 10(3):165-77.
14. Wolf MS, Feinglass J, Thompson J, Baker DW. In search of 'low health literacy': threshold vs. gradient effect of literacy on health status and mortality. *Soc Sci Med*. 2010;70(9):1335-41.
15. Wolf MS, Davis TC, Shrank W, Rapp DN, Bass PF, Connor UM, et al. To err is human: patient misinterpretations of prescription drug label instructions. *Patient Educ Couns*. 2007;67(3):293-300.
16. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc.* 2011;86(4):304-14.
17. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care.* 2005; 43(6):521-30.
18. Roebuck MC, Dougherty JS. Impact of medication adherence on hospitalization in Medicaid. *Value Health*. 2016;19(3):A9.
19. Puspitasari HP, Aslani P, Krass I. A review of counseling practices on prescription medicines in community pharmacies. *Res Soc Adm Pharm.* 2009; 5(3):197-210.
20. Rajda C, George NM. The effect of education and literacy levels on health outcomes of the elderly. *J Nurse Pract*. 2009;5(2):115-9.
21. Kessels RPC. Patients' memory for medical information. *J R Soc Med.*2003; 96(5):219-22.
22. Pires C, Vigário M, Cavaco A. Readability of medicinal package leaflets: a systematic review. *Rev Saude Publica*. 2015;49:4.
23. Wolf MS, King J, Wilson EAH, Curtis LM, Bailey SC, Dhuig J, et al. Usability of FDA-approved medication guides. *J Gen Intern* Med.2012; 27(12):1714-20.
24. Liu F, Abdul-Hussain S, Mahboob S, Rai V, Kostrzewski A. How useful are medication patient information leaflets to older adults? A content, readability and layout analysis. *Int J Clin Pharm*. 2014;36(4):827-34.
25. Readdean KC, Heuer AJ, Parrott JS. Effect of pharmacist intervention on improving antidepressant medication adherence and depression symptomology: a systematic review and meta-analysis. *Res Soc Adm Pharm.* 2018; 14(4);321-31.
26. van Eikenhorst L, Taxis K, van Dijk L, de Gier H. Pharmacist-led self-management interventions to improve diabetes outcomes. A systematic literature review and meta-analysis. *Front Pharmacol.* 2017;8:891.
27. Hesso I, Gebara SN, Kayyali R. Impact of community pharmacists in COPD management: inhalation technique and medication adherence. *Respir Med.* 2016;118:22-30.
28. Bukhsh A, Khan TM, Lee SWH, Lee LH, Chang KG, Goh BH. Efficacy of pharmacist based diabetes educational interventions on clinical outcomes of adults with type 2 diabetes mellitus: a network meta-analysis. *Front Pharmacol.* 2018;9:339.
29. Cheema E, Sutcliffe P, Singer DRJ. The impact of interventions by pharmacists in community pharmacies on control of hypertension: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol.* 2014;78(6):1238-47.
30. Peregrin T. Picture this: visual cues enhance health education messages for people with low literacy skills. *J Am Diet Assoc*. 2010;110(4):500,502-5.
31. Del Re L, Vaillancourt R, Villarreal G, Pouliot A. Pictograms: can they help patients recall medication safety instructions? *Visible Lang.* 2016; 50(1):127-51.
32. Ng AWY, Chan AHS, Ho VWS. Comprehension by older people of medication information with or without supplementary pharmaceutical pictograms. *Appl Ergon*. 2017;58:167-75.

33. Mullen RJ, Duhig J, Russell A, Scarazzini L, Lievano F, Wolf MS. Best-practices for the design and development of prescription medication information: a systematic review. *Patient Educ Couns.* 2018;101(8):1351-67.
34. Dowse R, Ehlers M. Medicine labels incorporating pictograms: do they influence understanding and adherence? *Patient Educ Couns.* 2005;58(1): 63-70.
35. Chan HK, Hassali MA. Modified labels for long-term medications: influences on adherence, comprehension and preferences in Malaysia. *Int J Clin Pharm*. 2014;36(5):904-13.
36. Mansoor L, Dowse R. Written medicines information for South African HIV/AIDS patients: does it enhance understanding of co-trimoxazole therapy? *Health Educ Res*. 2007;22(1):37-48.
37. Wilby K, Marra CA, da Silva JH, Grubisic M, Harvard S, Lynd LD. Randomized controlled trial evaluating pictogram augmentation of HIV medication information. *Ann Pharmacother*. 2011;45(11):1378-83.
38. Malhotra R, Bautista MAC, Tan NC, Tang WE, Tay S, Tan S, et al. Bilingual text with or without pictograms improves elderly Singaporeans' understanding of prescription medication labels. *Gerontologist*. 2019;59(2):378-90.
39. You WB, Grobman W, Davis T, Curtis LM, Bailey SC, Wolf M. Improving pregnancy drug warnings to promote patient comprehension. *Am J Obstet Gynecol*. 2011;204(4):318.e1-5.
40. Advani AA, Lopez J, Jones J, Patel S. The role of pictograms for enhancement of patient prescription medication information. *J Pharm Technol.* 2013; 29(1):40-5.
41. Wolf MS, Davis TC, Bass PF, Curtis LM, Lindquist LA, Webb JA, et al. Improving prescription drug warnings to promote patient comprehension. *Arch Intern Med*. 2010;170(1):50-6.
42. van Beusekom MM, Kerkhoven AH, Bos MJW, Guchelaar HJ, van den Broek JM. The extent and effects of patient involvement in pictogram design for written drug information: a short systematic review. *Drug Discov Today.* 2018;23(6):1312-8.
43. Sorfleet C, Vaillancourt R, Groves S, Dawson J. Design, development and evaluation of pictographic instructions for medications used during humanitarian missions. *Can Pharm J.* 2009;142(2):82-8.
44. Zargarzadeh AH, Ahamdi S. Comprehensibility of selected USP pictograms by illiterate and literate Farsi speakers: the first experience in Iran - part I. *J Res Med Sci.* 2017;22:84.
45. Zargarzadeh AH, Ahamdi S. Comprehensibility of selected United States Pharmacopeia pictograms by illiterate and literate Farsi speakers: the first experience in Iran – part II. *J Res Med Sci*. 2017;22:101.
46. Barros IMC, Alcântara TS, Mesquita AR, Bispo ML, Rocha CE, Moreira VP, et al. Understanding of pictograms from the United States Pharmacopeia Dispensing Information (USP-DI) among elderly Brazilians. *Patient Prefer Adherence*. 2014;8:1493-501.
47. Dowse R, Ehlers M. Pictograms for conveying medicine instructions: comprehension in various South African language groups. *S Afr J Sci.* 2004; 100:687-93.
48. Kassam R, Vaillancourt R, Collins JB. Pictographic instructions for medications: do different cultures interpret them accurately? *Int J Pharm Pract.* 2004;12(4):199-209.
49. Merks P, SwSieczkowski D, Balcerzak M, Drelich E, Białoszewska K, Cwalina N, et al. The evaluation of pharmaceutical pictograms among elderly patients in community pharmacy settings – a multicenter pilot study. *Patient Prefer Adherence.* 2018;12:257-66.
50. Vaillancourt R, Pouliot A, Streitenberger K, Hyland S, Thabet P. Pictograms for safer medication management by health care workers. *Can J Hosp Pharm.* 2016;69(4):286-93.
51. Berthenet M, Vaillancourt R, Pouliot A. Evaluation, modification, and validation of pictograms depicting medication instructions in the elderly. *J Health Commun*. 2016;21 Suppl 1:27-33.
52. van Beusekom MM, Land-Zandstra AM, Bos MJW, van den Broek JM, Guchelaar HJ. Pharmaceutical pictograms for low-literate patients: understanding, risk of false confidence, and evidence-based design strategies. *Patient Educ Couns.* 2017;100(5):966-73.
53. Kheir N, Awaisu A, Radoui A, El Badawi A, Jean L, Dowse R. Development and evaluation of pictograms on medication labels for patients with limited literacy skills in a culturally diverse multiethnic population. *Res Social Adm Pharm*. 2014;10(5):720-30.
54. Joshi Y, Kothiyal P. A pilot study to evaluate pharmaceutical pictograms in a multispecialty hospital at Dehradun. *J Young Pharm*. 2011;3(2):163-6.
55. Cutler TW, Chuang A, Huynh TD, Witt RG, Branch J, Pon T, et al. A retrospective descriptive analysis of patient adherence to dabigatran at a large academic medical center. *J Manag Care Spec Pharm*. 2014;20(10):1028-34.
56. Chuang MH, Lin CL, Wang YF, Cham TM. Development of pictographs depicting medication use instructions for low-literacy medical clinic ambulatory patients. *J Manag Care Spec Pharm.* 2016;16(5):337-45.
57. Korenevsky A, Vaillancourt R, Pouliot A, Revol M, Steed E, Besançon L, et al. How many words does a picture really tell? Cross-sectional descriptive study of pictogram evaluation by youth. *Can J Hosp Pharm.* 2013;66(4): 219-26.
58. Revol M, Vaillancourt R, Pouliot A. Evaluation, validation, and modification of pictograms depicting potential side effects to medication. *J Commun Healthc*. 2013;6(2):79-89.
59. Yu B, Willis M, Sun P, Wang J. Crowdsourcing participatory evaluation of medical pictograms using Amazon Mechanical Turk. *J Med Internet Res.* 2013;15(6):e108.
60. Chan AHS, Chan KWL. Effects of prospective-user factors and sign design features on guessability of pharmaceutical pictograms. *Patient Educ Couns.* 2013;90(2):268-75.
61. Soares MA. Legibility of USP pictograms by clients of community pharmacies in Portugal. *Int J Clin Pharm*. 2013;35(1):22-9.
62. Richler M, Vaillancourt R, Celetti SJ, Besançon L, Arun KP, Sebastien F. The use of pictograms to convey health information regarding side effects and/or indications of medications. *J Commun Healthc.* 2012;5(4):220-6.
63. Knapp P, Raynor DK, Jebar AH, Price SJ. Interpretation of medication pictograms by adults in the UK. *Ann Pharmacother*. 2005;39(7-8):1227-33.
64. Wilson EAH, Vaillancourt R, Pascuet E, Besançon LJR, Wolf MS. Seeking international consensus in the use of icons for medication instructions. *J Commun Heal*. 2012;5(1):67-72.
65. Technical Committee ISO/TC 145 Graphical Symbols. *ISO 9186-1:2014. Graphical symbols — test methods — part I: method for testing comprehensibility*. Geneva (CH): International Organization for Standardization; 2014.
66. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The Mini-Cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry.* 2000;15(11):1021-7.
67. Carmeli S, Shen Y. Semantic transparency and translucency in compound blissymbols. *Augment Altern Commun*. 1998;14(3):171-83.
68. *Visual census. 2011 Census*. Ottawa (ON): Statistics Canada; 2012.
69. *FIP guidelines for the labels of prescribed medicines*. The Hague (Netherlands): International Pharmaceutical Federation; 2001.
70. Houts PS, Witmer JT, Egeth HE, Loscalzo MJ, Zabora JR. Using pictographs to enhance recall of spoken medical instructions II. *Patient Educ Couns.* 2001;43(3):231-42.
71. Paivio A. I*magery and verbal processes*. Oxford (UK): Holt, Rinehart and Winston; 1971.
72. De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). *Ann Intern Med*, 2018;169(1):30-5.

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Implementation of a Clinical Decision Support Tool to Improve Antibiotic IV-to-Oral Conversion Rates at a Community Academic Hospital

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ABSTRACT

Background: Antibiotic IV-to-oral (IV–PO) conversion is a key initiative of antimicrobial stewardship programs. Guidelines and education are commonly described interventions to promote IV–PO conversion; however, technological interventions may be more effective in changing practice.

Objective: To determine the impact of a clinical decision support (CDS) tool on the adoption and sustainability of an antibiotic IV–PO conversion program at a community academic hospital.

Methods: A quasi-experimental study consisting of 3 phases was conducted. During phase 1, the pre-intervention antibiotic IV–PO conversion rate was determined. During phase 2, the IV–PO conversion policy was updated, education was provided to pharmacists and physicians, and a post-intervention evaluation was conducted. During phase 3, a CDS tool was developed to generate real-time electronic alerts prompting pharmacists to assess antibiotic therapy, and post-intervention audits were performed 1 month, 3 months, and 15 months after implementation of the tool. Pantoprazole IV–PO conversion was assessed during each phase as a non-equivalent dependent variable. The primary outcome was the proportion of patients eligible for IV–PO conversion who were switched to oral therapy.

Results: Of 332 patients receiving targeted IV antibiotic therapy during the overall study period, 122 (37%) met the criteria for IV–PO conversion. The phase 2 IV–PO conversion rate of 35% (9/26) was comparable to the pre-intervention rate of 29% (10/35) ($p = 0.61$). Implementation of the CDS tool significantly increased the conversion rate to 78% (14/18), an increase that was sustained at 3 months (71% [17/24]) and 15 months (74% [14/19]) after implementation ($p < 0.05$ for all comparisons with phases 1 and 2). Pantoprazole conversion rates were similar across all phases.

Conclusions: Implementation of the CDS tool was effective in improving and sustaining antibiotic IV–PO conversion rates and enhancing policy compliance beyond the effects of policy revision and education. Refinement of both the policy and the tool is warranted to maximize adoption of the IV–PO conversion program.

RÉSUMÉ

Contexte: Le passage de l'antibiothérapie par voie intraveineuse (IV) à la voie orale (PO) (IV-PO) est une initiative clé des programmes de gestion des antimicrobiens. On a communément recours à des formations et à des lignes directrices pour encourager le passage d'une voie à l'autre; cependant, les interventions technologiques sont parfois plus efficaces pour favoriser le changement de pratique.

Objectif : Déterminer l'impact d'un outil d'aide à la décision clinique (ADC) sur l'adoption et la viabilité d'un programme de conversion IV-PO dans un hôpital universitaire.

Méthodes : Une étude quasi expérimentale en trois phases a été menée. La première phase a permis la détermination du taux de conversion IV-PO avant l'intervention. La deuxième phase concernait l'actualisation de la politique de conversion IV-PO, la formation des pharmaciens et médecins et la conduite d'une évaluation après l'intervention. La troisième phase a vu le développement d'un outil ADC qui génère des alertes électroniques en temps réel pour inciter les pharmaciens à évaluer l'antibiothérapie. Des évaluations ont en outre été effectuées 1 mois, 3 mois et 15 mois après la mise en place de l'outil. Le passage de l'administration du pantoprazole par voie intraveineuse (IV) à voie orale (PO) a été évalué au cours de chaque phase comme une variable dépendante non équivalente. Le résultat principal fut la proportion de patients admissibles à la conversion IV–PO qui ont été orientés vers un traitement par voie orale.

Résultats : Des 332 patients recevant une antibiothérapie ciblée par voie intraveineuse (IV) pendant l'étude, 122 (37 %) répondaient au critère de la conversion IV–PO. Le taux de conversion IV–PO de 35 % (9/26) de la phase 2 était comparable au taux avant l'intervention de 29 % (10/35) ($p = 0{,}61$). La mise en place de l'outil ADC a grandement augmenté le taux de conversion, qui est passé à 78 % (14/18) : une augmentation maintenue trois mois (71 % [17/24]) et 15 mois (74 % [14/19]) après la mise en place ($p < 0{,}05$ par rapport aux phases 1 et 2). Les taux de conversion du pantoprazole étaient similaires durant toutes les phases.

Conclusions : La mise en place de l'outil ADC a permis d'améliorer et de maintenir les taux de conversion IV–PO et de renforcer le respect des

Keywords: antimicrobial stewardship, clinical decision support systems, IV-to-oral conversion, antimicrobials, pharmacists

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politiques au-delà des effets de la révision des politiques et de la formation à celles-ci. Le perfectionnement de la politique et de l'outil se justifie pour maximiser l'adoption du programme de conversion IV–PO.

Mots-clés : gestion de l'utilisation des antimicrobiens, systèmes d'aide à la décision clinique, passage de la voie intraveineuse (IV) à la voie orale (PO), antimicrobiens, pharmaciens

INTRODUCTION

Antibiotic IV-to-oral (IV–PO) conversion is a key initiative of antimicrobial stewardship programs. Transitioning patients from IV to oral antibiotics when it is appropriate to do so has several advantages, including decreasing the risk of catheter-related infections, shortening the length of hospital stay, and decreasing health care costs.[1-4] Considering the clinical and cost benefits, IV–PO conversion programs are strongly recommended by antimicrobial stewardship implementation guidelines[5,6] and are promoted in the Choosing Wisely Canada campaign.[7]

Guidelines, education, and non-technological interventions have traditionally been the primary means of facilitating IV–PO conversion[8-11]; however, technological interventions based on human factors engineering principles are viewed as more effective in changing behaviours and practices.[12] There is a growing call for the integration of computerized clinical decision support (CDS) systems in antimicrobial stewardship programs to improve antibiotic prescribing practices and to enhance the implementation and sustainability of initiatives.[5,7,13,14] These systems use patient data and clinical knowledge to provide patient-specific recommendations that aid health care providers in clinical decision-making at the point of care.[13] Therefore, guidelines and education paired with CDS tools could represent a more effective approach to promoting IV–PO conversion.

A quality improvement study, with the ultimate goal of enhancing adoption of an IV–PO conversion program, was undertaken between 2013 and 2016 at a community academic hospital. At the study institution, a pharmacist-initiated, criteria-based IV–PO conversion policy had been in place since 2007. The current study involved a stepwise approach, beginning with an update to the policy accompanied by staff education, followed by development and implementation of a CDS tool, with evaluation of IV-PO conversion rates after each intervention. The objective of this study was to determine the impact of the CDS tool on the adoption and sustainability of the antibiotic IV–PO conversion program at the study institution.

METHODS

Study Design

A quasi-experimental study was conducted at a 420-bed community academic hospital in Toronto, Ontario, Canada. The institution is a single-site hospital that provides a range of acute care and ambulatory services, with an off-site long-term care centre. The hospital uses an electronic medical record system (Cerner Corporation, Kansas City, Missouri) that integrates computerized physician order entry, medication administration, clinical documentation, and CDS capabilities. The hospital has an established antimicrobial stewardship program involving an infectious diseases physician (P.D.) and 2 pharmacists (T.K., S.R.), who perform prospective audit and feedback for hospital inpatients within the medicine program.

The study consisted of 3 phases: the pre-intervention period (July and August 2013); policy revision and staff education, with post-intervention evaluation (May and June 2014); and development and implementation of a CDS tool, with post-intervention evaluation (October 2014 to January 2016). Adult patients (≥18 years) admitted on 5 general medicine and surgical units were reviewed for eligibility and inclusion in the study. The study protocol received approval from the institutional research ethics board.

Phase 1: Pre-intervention

The first iteration of the IV–PO conversion policy at the hospital was introduced in 2007. The policy covers 9 targeted IV antibiotic agents (Table 1) and 2 non-antibiotic agents (pantoprazole and ranitidine). The policy allows for pharmacists to automatically switch a targeted IV antibiotic agent to oral therapy if specific criteria are met (Table 2). The criteria for IV–PO conversion of the non-antibiotic agents are the patient being able to tolerate oral medications and the patient continuing to need the medication for a specified indication. A baseline (pre-intervention) assessment of the antibiotic IV–PO conversion rate was conducted.

Table 1. Targeted IV Antibiotics with Corresponding Oral Antibiotic after Conversion

IV Antibiotic	Oral Antibiotic after Conversion
ampicillin	amoxicillin
azithromycin	azithromycin
cefazolin	cephalexin
cefuroxime	cefuroxime
ciprofloxacin	ciprofloxacin
clindamycin	clindamycin
levofloxacin	levofloxacin
metronidazole	metronidazole
penicillin G	penicillin VK

Phase 2: Policy Revision and Staff Education

The next phase of the study focused on revision of the IV–PO policy to reflect workflow changes and provision of staff education to improve adoption of the IV–PO program. Implementation of the policy in 2007 occurred before establishment of an electronic medical record system at the hospital, which occurred in 2010; therefore, the policy required revisions to reflect the transition from a paper-based practice to an electronic workflow. Specifically, procedures for electronic documentation of pharmacists' assessments of IV–PO conversion for individual patients and electronic communication of these assessments to the health care team were incorporated into the policy, with approval from the institution's pharmacy and therapeutics committee. Apart from these revisions in the procedure, the policy remained the same; specifically, there were no changes to eligibility criteria or the targeted IV medication list. Staff education was then provided to both pharmacists and physicians to increase policy awareness and improve policy adoption. The antimicrobial stewardship pharmacists delivered an education session to the pharmacists and provided a pocket reference guide reviewing the principles of IV–PO conversion and the institution's IV–PO policy. The antimicrobial stewardship pharmacists also delivered a separate presentation to physicians within the medicine program regarding the general principles of IV–PO conversion and the institutional policy. A post-intervention audit of the IV–PO conversion rate was performed 1 month after the delivery of education. Pharmacists' and physicians' knowledge and awareness of IV–PO conversion were not directly assessed.

Phase 3: Development and Implementation of CDS Tool

Following the delivery of staff education and assessment of its effectiveness, a CDS tool to facilitate antibiotic IV–PO conversion was developed by the antimicrobial stewardship pharmacists, working in collaboration with a consultant from the hospital's clinical informatics team. This criteria-based tool, which is embedded within the Cerner electronic medical record system, identifies patients who are potentially eligible for antibiotic IV–PO conversion and generates real-time electronic alerts to prompt a pharmacist's assessment. An alert is generated if all of the following criteria are met: the patient is receiving a targeted IV antibiotic, the antibiotic order has been active for at least 48 h, the antibiotic order does not have a fixed duration, there is no documented fever (i.e., no temperature measurements > 37.6°C) in the past 24 h, and the patient has an order for an oral diet. The third criterion, which excludes orders with a fixed duration, was a practical consideration to reduce the risk of alert fatigue. At the study hospital, most antibiotic orders with a fixed duration are for surgical prophylaxis; these orders generally have a fixed duration of 24 h and are automatically discontinued after this period has elapsed. The exclusion of this type of order was intended to improve the specificity of the CDS alert.

Once all of the criteria are met for a particular patient, a real-time electronic alert is automatically generated and integrated into the unit pharmacist's daily electronic task list. The unit pharmacist then assesses the patient and proceeds with IV–PO conversion if appropriate. Before hospital-wide implementation of the CDS tool, an education session was provided to the pharmacists to discuss features of the CDS tool and the associated workflow. Post-intervention audits were performed at 1 month (phase 3a), 3 months (phase 3b), and 15 months (phase 3c) after CDS implementation to determine the tool's impact on the sustainability of the IV–PO conversion program.

Table 2. Criteria for Pharmacist-Initiated Antibiotic IV-to-Oral Conversion*

Inclusion Criteria	Exclusion Criteria
All inclusion criteria must be met for the patient to be eligible for IV-to-oral conversion: • The patient has a functioning gastrointestinal tract and is tolerating oral medications • The patient is showing clinical improvement and has been afebrile for 24 h • The patient continues to need the antibiotic for treatment of the infectious disease (as documented in the patient's medical chart by the most responsible physician)	The presence of any exclusion criterion would result in patient's exclusion from eligibility for IV-to-oral conversion: • The patient has an infectious disease for which oral therapy would be inappropriate (e.g., endocarditis, *Staphylococcus aureus* bacteremia, meningitis) • The patient has a "nothing by mouth" order • The patient has neutropenia

*The criteria outlined here were in place before the current study began.

Data Collection

During each phase of the study, chart audits were conducted over a 6-week evaluation period on 5 general medicine and surgical units. All patients on these units who were receiving targeted IV antibiotics were included in the audits. The following de-identified data were collected: patient age and sex, type of infectious disease, and current antibiotic regimen. Eligibility for IV–PO conversion was determined according to the policy's criteria, and conversion to oral therapy was checked. Pantoprazole IV–PO conversion was assessed concurrently during each phase as a non-equivalent dependent variable. Patients receiving IV pantoprazole were identified, their eligibility for IV–PO conversion was determined, and conversion to oral therapy was checked.

Outcomes and Statistical Analysis

Descriptive statistics were calculated for all variables of interest. Categorical variables were summarized using counts and percentages. Continuous variables were summarized as the mean with standard deviation or as the median with interquartile range (IQR).

The primary outcome was the proportion of patients eligible for antibiotic IV–PO conversion who were switched to oral therapy. The secondary outcome was the duration of IV therapy until the switch to oral therapy. A non-equivalent dependent variable, pantoprazole IV–PO conversion, was included in the study to increase the validity of the results.[15] Pantoprazole was a targeted medication under the institutional IV–PO conversion policy. However, the study interventions (staff education and CDS implementation) were not directed at improving conversion to oral therapy for non-antibiotic medications. Instead, staff education focused on antibiotic IV–PO conversion, and the CDS tool assessed the potential for IV–PO conversion for targeted antibiotics only. Therefore, it was hypothesized that rates of antibiotic IV–PO conversion would increase following the interventions, whereas rates of pantoprazole IV–PO conversion would remain unchanged.

Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the t test. All effects were considered significant at p less than 0.05. All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Over the entire study, a total of 332 patients who were receiving targeted IV antibiotics were reviewed for eligibility for IV–PO conversion, of whom 122 patients (37%) met the eligibility criteria; baseline characteristics of these patients are summarized in Table 3.

Antibiotic IV–PO conversion rates during all phases are shown in Figure 1. During phase 1, the pre-intervention phase, 10 (29%) of 35 eligible patients were switched to oral therapy. Following policy revision and staff education (phase 2), 9 (35%) of 26 eligible patients were switched to oral therapy, which was comparable to the rate in phase 1 ($p = 0.61$). Following implementation of the CDS tool, the proportion of eligible patients switched to oral therapy increased significantly to 14 (78%) of 18 patients at 1 month after implementation (phase 3a: $p = 0.001$ compared with phase 1; $p = 0.006$ compared with phase 2). This

Table 3. Baseline Characteristics of Patients Who Met Eligibility Criteria for Antibiotic IV-to-Oral Conversion

Variable	Phase; No. (%) of Patients*				
	Phase 1: Pre-intervention (*n* = 35)	Phase 2: Policy and Education (*n* = 26)	Phase 3a: 1 month after CDS (*n* = 18)	Phase 3b: 3 months after CDS (*n* = 24)	Phase 3c: 15 months after CDS (*n* = 19)
Age (years) (median and IQR)	72 (55–84)	73 (59–87)	86 (78–89)	71 (59–88)	79 (52–88)
Sex, female	15 (43)	13 (50)	8 (44)	21 (88)	11 (58)
Infectious disease					
Respiratory	15 (43)	6 (23)	3 (17)	13 (54)	4 (21)
Intra-abdominal	13 (37)	7 (27)	5 (28)	5 (21)	7 (37)
Skin and soft tissue	6 (17)	5 (19)	7 (39)	3 (13)	3 (16)
Urinary	1 (3)	8 (31)	3 (17)	3 (13)	5 (26)
Targeted IV antibiotic†	*n* = 38	*n* = 30	*n* = 20	*n* = 25	*n* = 22
Ampicillin	0	4 (13)	1 (5)	1 (4)	3 (14)
Azithromycin	6 (16)	4 (13)	1 (5)	9 (36)	1 (5)
Cefazolin	8 (21)	11 (37)	8 (40)	4 (16)	6 (27)
Ciprofloxacin	2 (5)	3 (10)	3 (15)	2 (8)	3 (14)
Levofloxacin	8 (21)	2 (7)	2 (10)	4 (16)	2 (9)
Metronidazole	14 (37)	6 (20)	5 (25)	5 (20)	7 (32)

CDS = clinical decision support, IQR = interquartile range
*Except where indicated otherwise.
†Patients may have been receiving more than 1 targeted IV antibiotic concurrently; percentages in this section are calculated in relation to the total number of antibiotic prescriptions.

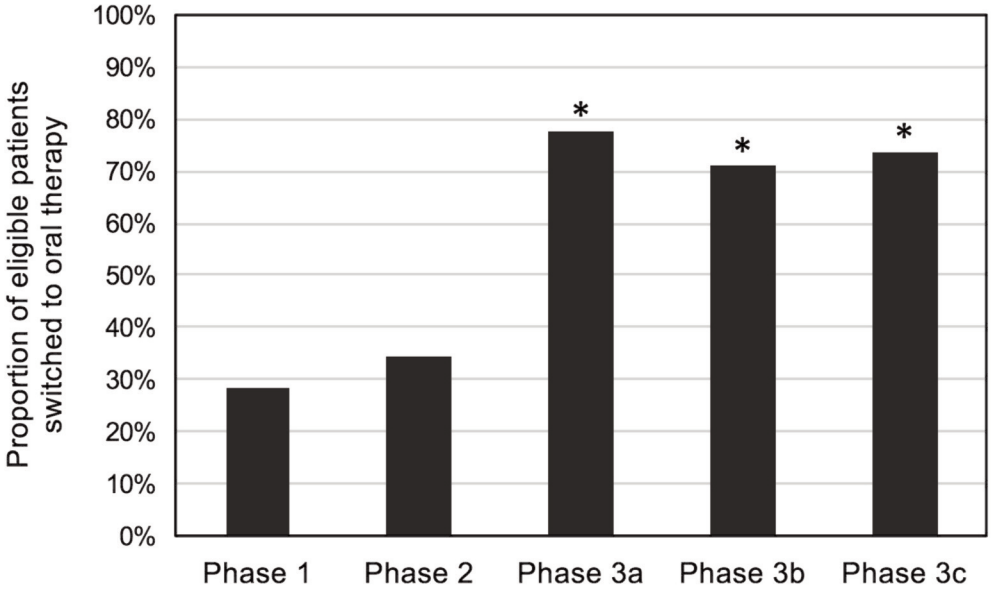

Figure 1. Proportion of eligible patients who were switched to oral therapy in the pre-intervention period (phase 1), after the education intervention (phase 2), 1 month after implementation of the clinical decision support (CDS) tool (phase 3a), 3 months after implementation of the CDS tool (phase 3b), and 15 months after implementation of the CDS tool (phase 3c). *Statistically significant difference, compared with phase 1 and phase 2 ($p < 0.05$ for all comparisons with phases 1 and 2).

improvement was sustained with 17 (71%) of 24 patients being switched to oral therapy at 3 months after CDS implementation, and 14 (74%) of 19 patients being switched to oral therapy at 15 months after implementation (phases 3b and 3c, respectively: $p = 0.001$ for both compared with phase 1; $p = 0.01$ for both compared with phase 2). All of the patients who were switched to oral therapy completed their antibiotic course with oral therapy and did not require transition back to IV therapy. With regard to the non-equivalent dependent variable, pantoprazole IV–PO conversion rates were similar across all phases: 18 (58%) of 31 patients in phase 1, 19 (63%) of 30 patients in phase 2, 33 (69%) of 48 patients in phase 3a, 12 (60%) of 20 patients in phase 3b, and 17 (63%) of 27 patients in phase 3c (all $p > 0.30$ compared with phase 1). The median duration of IV antibiotic therapy before IV–PO conversion was similar across all phases: 3 days (IQR 3–4) in phases 1, 2, 3a, and 3b, and 4 days (IQR 3–5) in phase 3c.

During the CDS implementation phase (phase 3), electronic alerts were generated for 186 patients, of whom 61 (33%) fulfilled all criteria for IV–PO conversion. The main reasons for ineligibility were the type of infectious disease precluding pharmacist-initiated IV–PO conversion (for 55 patients) and the antibiotic no longer being indicated (for 36 patients). The median duration from initiation of IV antibiotic therapy to generation of an electronic alert was 2 days. For eligible patients in this phase, a total of 67 courses of targeted IV antibiotic therapy met conversion criteria, of which 17 were not converted (8 courses of metronidazole, 5 courses of azithromycin, and 4 courses of cefazolin).

DISCUSSION

In this study, the implementation of a CDS tool to facilitate antibiotic IV–PO conversion was associated with a doubling of IV–PO conversion rates relative to the combination of a policy update and education. Pantoprazole IV–PO conversion rates were similar across all phases, which suggests that the improvement in antibiotic conversion was attributable to implementation of the CDS tool. Antimicrobial stewardship activities, such as prospective audit and feedback, remained unchanged during the study period, further supporting the conclusion that improvements in compliance were attributable to the CDS tool.

There is a lack of comparative data to indicate the type of intervention that is most effective in optimizing and sustaining IV–PO conversion programs. This is the first study of which we are aware that assessed the effectiveness of stepwise implementation of a pair of non-technological interventions (policy implementation and staff education) and a technological intervention. We observed only minimal improvements in IV–PO conversion rates with the policy update and associated education, whereas the technological intervention proved far more

effective in improving program uptake. In addition, this study demonstrated long-term program sustainability with use of the CDS tool, with sustained improvements in IV–PO conversion rates at 3 and 15 months after implementation. Previous studies have documented successes with guideline implementation, education, and printed checklists and information sheets[8-11]; however, data supporting the long-term sustainability of these interventions are lacking. One study that used guidelines and education was unable to demonstrate a sustained improvement in IV–PO conversion rates 3 months after implementation.[16] Person-based strategies, such as policies and education, that are implemented in isolation often do not produce long-term sustainable benefits, and system-based strategies may be required.[17] Therefore, implementation of CDS tools complementary to policy and education may be necessary to achieve sustained improvements.

Despite the multipronged approach to improving IV–PO program uptake, including CDS implementation, IV–PO conversion rates remained steady during phase 3 of our study, at about 75%. This may point to a need to further refine the IV–PO policy. For example, the policy currently outlines infectious disease syndromes for which IV–PO conversion is inappropriate; however, there may be a lack of clarity regarding the clinical situations that are suitable for conversion. Specifying the indications for which IV–PO conversion would be appropriate may lead to better policy compliance. Another reason for not transitioning eligible patients to oral therapy was use of combination antibiotic regimens in which only one of the antibiotics was covered by the IV–PO policy. Azithromycin and metronidazole were both included in the list of antibiotics targeted for conversion in the institutional policy, but in most cases of non-conversion of these 2 antibiotics in phase 3 (11/13), conversion did not occur because the azithromycin or metronidazole was being administered in combination with ceftriaxone, which is not included in the list of targeted antibiotics. Although combination antibiotic therapy was not a criterion for exclusion from IV–PO conversion, pharmacists may have been hesitant to partially convert these regimens (by changing only 1 of the 2 drugs from IV to oral administration). Recent antimicrobial stewardship recommendations promote interventions for certain infectious disease syndromes,[5,6] and we are considering adding syndrome-specific IV–PO conversion recommendations into the policy to further improve conversion rates.

There is growing interest in leveraging technology to facilitate and enhance sustainability of antimicrobial stewardship initiatives. Previous studies have described computerized IV–PO alerts, which generally assess whether a patient is receiving a targeted medication and whether medications or diet is being administered orally.[18-20] More recently, a physician-targeted CDS alert that assessed more parameters, including presence of fever and neutrophilia, has been described. This intervention was associated with a decrease in duration of IV therapy.[21] Our CDS tool similarly incorporated more complex rules to identify with greater specificity those patients who are eligible for IV–PO conversion; it also targeted pharmacists rather than physicians. Pharmacists play a central role in medication review and IV–PO conversion, and previous studies have demonstrated the effectiveness of pharmacist-managed IV–PO conversion programs.[3,4]

We are continuing to refine the CDS tool to enhance its effectiveness and usability. Our analysis showed that only 33% of patients for whom an electronic alert was generated fulfilled all criteria for IV–PO conversion, which raises a concern about alert fatigue.[14] The main reasons for ineligibility for IV–PO conversion were presence of a type of infectious disease that precluded pharmacist-initiated IV-PO conversion (as specified by the policy's exclusion criteria) and antibiotics no longer being indicated. There is increasing interest in indication-based prescribing to improve medication safety and prescribing practices.[22] Our institution currently does not incorporate the indication into medication orders; however, inclusion of such a parameter could improve the CDS tool's specificity, decrease the proportion of non-actionable alerts, and reduce the risk of alert fatigue. Other considerations for improvement involve reassessing the criteria for generating an alert. The CDS tool currently excludes fixed-duration antibiotic orders; however, this exclusion could lead to potentially eligible IV antibiotic orders being overlooked, especially with antimicrobial stewardship programs' increasing emphasis on optimizing antibiotic durations.[5] Removing this exclusion could potentially increase the sensitivity of the tool. Furthermore, it was noted that the time to IV–PO conversion remained unchanged despite the study interventions, whereas previous studies have noted significant reductions in the duration of IV therapy before conversion.[2-4,8-11] In our CDS tool, the alert was generated when the antibiotic order had been active for at least 48 h, a threshold that was based on discussions with clinicians and a recognized timeframe for antimicrobial reassessment.[6] Shortening this timeframe for alert generation is a potential strategy to reduce the time to conversion.

Our study had several limitations. First, the study had a relatively small sample size, which was attributable to the short (6-week) evaluation periods (which were due, in turn, to resource limitations). Also, we did not account for potential seasonal variation in antibiotic prescribing because of the staggered time periods for each phase. Furthermore, our study was subject to the limitations inherent to quasi-experimental study designs, such as lack of randomization and difficulty controlling the confounding variables; however, we incorporated a non-equivalent dependent variable to increase the study validity.[15,23] In terms of the study outcomes, we focused on those that informed implementation and sustainability of the IV–PO conversion program, rather than on clinical and economic outcomes; benefits in these areas have been demonstrated in previous studies.[1-4,8-11] Indeed, it would have

been difficult to interpret clinical outcomes in this study, because of the aforementioned small sample size and difficulty in controlling for confounding factors. Finally, by their nature, chart reviews rely on documentation in existing medical records, which raises the risk of incomplete documentation and missing data.

CONCLUSION

The results of this study showed that implementation of a criteria-based CDS tool was effective in improving and sustaining antibiotic IV–PO conversion rates, while enhancing policy compliance beyond the effect of policy revision combined with education. Implementation of such a tool could be considered at other institutions to optimize antibiotic IV–PO conversion. Further refinement of the policy and the CDS tool is warranted to maximize antibiotic IV–PO program adoption.

References

1. Goff DA, Bauer KA, Reed EE, Stevenson KB, Taylor JJ, West JE. Is the "low-hanging fruit" worth picking for antimicrobial stewardship programs? *Clin Infect Dis*. 2012;55(4):587-92.
2. Davis SL, Delgado G, McKinnon PS. Pharmacoeconomic considerations associated with the use of intravenous-to-oral moxifloxacin for community-acquired pneumonia. *Clin Infect Dis.* 2005;41 Suppl 2:S136-43.
3. Kuti JL, Le TN, Nightingale CH, Nicolau DP, Quintiliani R. Pharmacoeconomics of a pharmacist-managed program for automatically converting levofloxacin route from i.v. to oral. *Am J Health Syst Pharm*. 2002; 59(22):2209-15.
4. Przybylski KG, Rybak MJ, Martin PR, Weingarten CM, Zaran FK, Stevenson JG, et al. A pharmacist-initiated program of intravenous to oral antibiotic conversion. *Pharmacotherapy*. 1997;17(2):271-6.
5. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America. *Clin Infect Dis*. 2016;62(10):e51-77.
6. Centers for Disease Control and Prevention. *Core elements of hospital antibiotic stewardship programs.* Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014 [cited 2019 Feb 18]. Available from: http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html
7. Leis JA, Evans GA, Ciccotelli W, Garber G, Gregson D, Lee TC, et al. Choosing Wisely Canada – top five list in infectious diseases: an official position statement of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. *J Assoc Med Microbiol Infect Dis Can*. 2016;1(1): 5-11.
8. Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, et al. Outcomes of early switching from intravenous to oral antibiotics on medical wards. *J Antimicrob Chemother.* 2009;64(1):188-99.
9. McLaughlin CM, Bodasing N, Boyter AC, Fenelon C, Fox JG, Seaton RA. Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: an intervention study. *Q J Med.* 2005;98(10):745-52.
10. Martinez MJ, Freire A, Castro I, Inaraja MT, Ortega A, Del Campo V, et al. Clinical and economic impact of a pharmacist-intervention to promote sequential intravenous to oral clindamycin conversion. *Pharm World Sci.* 2000;22(2):53-8.
11. Sevinc F, Prins JM, Koopmans RP, Langendijk PN, Bossuyt PM, Dankert J, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. *J Antimicrob Chemother.* 1999; 43(4):601-6.
12. Institute for Safe Medication Practices. Medication error prevention "toolbox". *ISMP Med Saf Alert.* 1999 Jun 2 [cited 2019 Nov 7]. Available from: https://www.ismp.org/resources/medication-error-prevention-toolbox
13. Pestotnik SL. Expert clinical decision support systems to enhance antimicrobial stewardship programs: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2005;25(8):1116-25.
14. Forrest GN, Van Schooneveld TC, Kullar R, Schulz LT, Duong P, Postelnick M. Use of electronic health records and clinical decision support systems for antimicrobial stewardship. *Clin Infect Dis.* 2014;59 Suppl 3:S122-33.
15. Harris AD, Bradham DD, Baumgarten M, Zuckerman IH, Fink JC, Perencevich EN. The use and interpretation of quasi-experimental studies in infectious diseases. *Clin Infect Dis.* 2004;38(11):1586-91.
16. van Niekerk AC, Venter DJ, Boschmans SA. Implementation of intravenous to oral antibiotic switch therapy guidelines in the general medical wards of a tertiary-level hospital in South Africa. *J Antimicrob Chemother.* 2012;67(3): 756-62.
17. Institute for Safe Medication Practices Canada. Designing effective recommendations. *Ont Crit Incident Learn*. 2013 [cited 2019 Nov 7]; 4:1-2. Available from: https://www.ismp-canada.org/download/ocil/ISMPCONCIL2013-4_EffectiveRecommendations.pdf
18. Galanter W, Liu XF, Lambert BL. Analysis of computer alerts suggesting oral medication use during computerized order entry of i.v. medications. *Am J Health Syst Pharm*. 2010;67(13):1101-5.
19. Fischer MA, Solomon DH, Teich JM, Avorn J. Conversion from intravenous to oral medications: assessment of a computerized intervention for hospitalized patients. *Arch Intern Med.* 2003;163(21):2585-9.
20. Glemaud I. Use of a physician order entry system to identify opportunities for intravenous to oral levofloxacin conversion. *Am J Health Syst Pharm*. 2000;57 Suppl 3:S14-6.
21. Beeler PE, Kuster SP, Eschmann E, Weber R, Blaser J. Earlier switching from intravenous to oral antibiotics owing to electronic reminders. *Int J Antimicrob Agents*. 2015;46(4):428-33.
22. Schiff GD, Seoane-Vazquez E, Wright A. Incorporating indications into medication ordering – time to enter the age of reason. *N Engl J Med.* 2016; 375(4):306-9.
23. Harris AD, Lautenbach E, Perencevich E. A systematic review of quasi-experimental study designs in the fields of infection control and antibiotic resistance. *Clin Infect Dis.* 2005;41(1):77-82.

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Stability of Inactivated Influenza Vaccine in Polypropylene Syringes under Various Storage Conditions

Influenza immunization is an effective strategy to reduce morbidity in health care providers and hospitalized patients.[1] When the vaccine is not provided in prefilled glass syringes, pharmacies prepare doses in polypropylene syringes, from multi-dose vials, to facilitate administration during vaccination campaigns. The *Canadian Immunization Guide* recommends delaying the process of loading syringes until it is time to vaccinate the patient, because of the lack of data about vaccine stability in syringes.[2] Data relating to room temperature storage are limited, and nonrefrigerated storage could result in reduced vaccine efficacy or adverse effects.[2,3] However, refrigerators may not be consistently available during vaccination campaigns. Previous reports suggested that an influenza vaccine in its original prefilled glass syringe packaging can be stored for a period from 72 h to 14 days at room temperature without any effect on product quality.[3,4] We sought to determine whether the influenza vaccine is stable in polypropylene syringes with refrigeration and at room temperature.

Vaccine stability testing includes determination of changes in vaccine structure, followed by immunologic assays to assess potency and biological activity.[5] In the hemagglutination (HA) assay, the hemagglutinin protein protruding from the influenza vaccine envelope binds to red blood cells, causing them to agglutinate.[6] This functional qualitative assay provides information about the physical stability of the vaccine.[7] The current study used the HA assay to evaluate the stability of hemagglutinin, in terms of binding to its receptor, after storage of vaccine in polypropylene syringes.

Samples of the inactivated split-virion, trivalent influenza vaccine for the 2016/2017 season in the northern hemisphere (GlaxoSmithKline Inc, Mississauga, Ontario; lot 22TC5, expiry May 2017) were loaded into polypropylene syringes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) and subjected to various storage conditions (all with protection from light). A 50-µL sample from each preparation was used to make serial 2-fold dilutions with phosphate-buffered saline in a 96-well round-bottom plate. Phosphate-buffered saline was used as the negative control, and freshly drawn-up vaccine was used as the positive control. Two drops of a 0.5% chicken red blood cell suspension were added to each well, and the plates were examined after 60 min at 4°C. A diffuse red layer at the bottom of the well was interpreted as indicating HA. In the absence of HA, the red blood cells settled as a "button". Results were recorded by the study investigators, who were blinded to storage conditions. Results of HA activity are reported as geometric mean titres (GMTs), defined as the inverse of the highest dilution with complete HA. The GMT is a sensitive parameter used in immunohematological studies to detect differences in antibody effects.[8,9] A GMT that is more than 2-fold lower than the positive control is interpreted as indicating a decrease in HA.[7]

Two groups of investigators completed the experiment (Table 1). As expected, heated samples did not display any HA. For samples stored at room temperature for 7 days, the HA GMT for group 2 suggests that titres dropped during the storage period, although a 4-fold decrease in HA titre was observed in only 1 of 6 samples overall. The GMTs after storage under other conditions (refrigerated storage for 72 h, followed by room temperature

Table 1. Hemagglutination Activity of Inactivated Influenza Vaccine Loaded in Polypropylene Syringes and Stored under Various Conditions, as Tested by 2 Investigator Groups

Storage Condition	Investigator Group 1		Investigator Group 2	
	No. of Samples	HA Titres (GMT and Range)	No. of Samples	HA Titres (GMT and Range)
Room temperature* for 7 days	3	5 161 (4 096–8 192)	3	813 (512–1 024)
Refrigerated† for 72 h, then room temperature* for 24 h	3	10 321 (8 192–16 384)	4	2 048 (2 048)
Refrigerated† for 72 h	3	5 161 (4 096–8 192)	4	1 722 (1 024–2 048)
Room temperature* for 30 h	3	5 161 (4 096–8 192)	3	1 024 (1 024)
Room temperature,* prepared morning of assay (positive control)	4	4 096 (2 048–8 192)	6	2 048 (2 048)
Heated‡ for 30 min	3	No HA	3	No HA

GMT = geometric mean titre, HA = hemagglutination.
*Room temperature: between 20°C and 25°C.
†Refrigeration: between 2°C and 8°C.
‡Heating: 80°C.

storage for 24 h; refrigerated storage for 72 h; and room temperature storage for 30 h) were comparable to the GMTs of samples prepared the morning of the experiment and held at room temperature.

The apparent decrease in HA titre after room temperature storage for 7 days may reflect recognized inter-rater variability in end-point detection of HA activity, or it may suggest that the structure of hemagglutinin is affected by extended exposure to room temperature. It would be of interest to test HA activity at intermediate times between 30 h and 7 days. However, storage in polypropylene syringes in select conditions (including refrigeration for 72 h and room temperature storage for 30 h) did not appear to reduce hemagglutinin activity, which indicates that storage in plastic did not lead to changes in protein structure. This finding suggests that potency would be retained, but quantitative serology assays, such as single radial immunodiffusion or viral neutralization assays, are required to confirm immunogenicity and clinical effect.[5] Other limitations of our study include the use of a single brand of influenza vaccine from one season and a single brand of syringes. Considering the available evidence, storage of influenza vaccine samples in polypropylene syringes under refrigeration for 72 h and up to 30 h at room temperature maintains the ability of hemagglutinin to bind to its receptor, suggesting preservation of protein structure. These storage conditions could therefore facilitate vaccine preparation and administration during vaccination campaigns.

References

1. Cortes-Penfield N. Mandatory influenza vaccination for health care workers as the new standard of care: a matter of patient safety and nonmaleficent practice. *Am J Public Health*. 2014;104(11):2060-5.
2. Public Health Agency of Canada. *Canadian immunization guide*. Ottawa (ON): Government of Canada; [updated 2017; cited 2017 Dec 22]. Available from: https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html
3. Cohen V, Jellinek SP, Teperikidis L, Berkovits E, Goldman WM. Room-temperature storage of medications labeled for refrigeration. *Am J Health Syst Pharm*. 2007;64(16):1711-5.
4. Coenen F, Tolboom JT, Frijlink HW. Stability of influenza sub-unit vaccine. Does a couple of days outside the refrigerator matter? *Vaccine*. 2006;24(4):525-31.
5. WHO Expert Committee on Biological Standardization. *Guidelines on stability evaluation of vaccines*. Geneva (CH): World Health Organization; 2011 [cited 2019 June 5]. Available from: https://www.who.int/biologicals/vaccines/Annex_3_WHO_TRS_962-3.pdf?ua=1
6. Eisfeld AJ, Neumann G, Kawaoka Y. Influenza A virus isolation, culture and identification. *Nat Protoc*. 2014;9(11):2663-81.
7. *Understanding influenza viruses: antigenic characterization*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases; 2017 [cited 2019 May 3]. Available from: https://www.cdc.gov/flu/about/viruses/index.htm
8. *Guidelines on clinical evaluation of vaccines: regulatory expectations*. Geneva (CH): World Health Organization; 2016 [cited 2019 May 3]. Available from: https://www.who.int/biologicals/expert_committee/Clinical_changes_IK_final.pdf
9. Leung VKY, Carolan LA, Worth LJ, Harper SA, Peck H, Tilmanis D, et al. Influenza vaccination responses: evaluating impact of repeat vaccination among health care workers. *Vaccine*. 2017;35(19):2558-68.

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For Patients Needing Oral Anticoagulation for Atrial Fibrillation and Dual Antiplatelet Therapy after Percutaneous Coronary Intervention, Is Double Therapy Preferred over Triple Therapy?

THE "PRO" SIDE

For many years clinicians have faced a conundrum in managing patients who require both oral anticoagulation and dual antiplatelet therapy after percutaneous coronary intervention (PCI). This scenario is commonly encountered in practice, given that approximately 20% of patients with atrial fibrillation will require PCI at some time, and up to 21% of patients with acute coronary syndrome (ACS) will also have new or established atrial fibrillation.[1,2] The need for triple therapy—that is, the use of an oral anticoagulant and dual antiplatelet therapy—has not been studied with rigour but has been adopted in practice, as there have been no perceived alternatives. However, cohort studies have shown that triple therapy leads to an increased risk of major bleeds.[3] We argue that there is now adequate evidence to avoid triple therapy and to change the standard of care for this population to double therapy, that is, the use of an anticoagulant (preferably a direct-acting oral anticoagulant) and a single antiplatelet agent (preferably a P2Y12 inhibitor).

The first study to investigate the use of double therapy was the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), published in 2013.[4] In this trial, patients (n = 573) who were receiving vitamin K antagonists and who underwent PCI were randomly assigned to receive acetylsalicylic acid (ASA) and clopidogrel (i.e., triple therapy) or clopidogrel alone (i.e., double therapy). At 1 year, the rate of major bleeding was 19.4% among those receiving double therapy and 44.4% for the triple-therapy group (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.25–0.50, $p < 0.0001$). With omission of the ASA there was no signal for loss of efficacy, given that the secondary combined end point of death, myocardial infarction, stroke, target vessel revascularization, and stent thrombosis was lower in the double-therapy group than in the triple-therapy group (11.1% versus 17.6%, adjusted HR 0.56, 95% CI 0.35–0.91). Of note, although the majority of patients (69%) were using anticoagulation for atrial fibrillation, patients with other indications (e.g., mechanical valve) were also included in this study.

The use of direct-acting oral anticoagulants in a double-therapy regimen was studied in a randomized controlled fashion in the PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicentre Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention).[5] Patients (n = 2124) with atrial fibrillation who underwent PCI were randomly assigned, within 3 days of the procedure, to receive 1 of the following 3 regimens: rivaroxaban 15 mg daily (or 10 mg daily if creatinine clearance was less than 50 mL/min) plus P2Y12 inhibitor; rivaroxaban 2.5 mg BID and dual antiplatelet therapy (for 1, 6, or 12 months); or triple therapy with warfarin. The primary outcome—bleeding that was clinically significant or required medical attention—was lower in both rivaroxaban groups than in the warfarin triple-therapy group (rivaroxaban 15 mg daily plus P2Y12 inhibitor: 16.8% versus 26.1%, HR 0.59, 95% CI 0.47–0.76, $p < 0.001$; rivaroxaban 2.5 mg BID plus dual antiplatelet therapy, 18.0% versus 26.7%, HR 0.63, 95% CI 0.50–0.80, $p < 0.001$). The rate of myocardial infarction, stroke, or death from cardiovascular causes was similar across all groups.[5]

Next, the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) randomly assigned patients (n = 2725) with atrial fibrillation within 5 days after PCI to receive either triple therapy with warfarin, a P2Y12 inhibitor, and ASA (with ASA being discontinued at 1 month for patients with bare metal stents or at 3 months for those with drug-eluting stents) or double therapy with dabigatran (110 or 150 mg BID) and P2Y12 inhibitor (clopidogrel or ticagrelor).[6] The primary end point (major or clinically relevant non-major bleeding) was significantly lower in the dual-therapy groups receiving dabigatran 150 mg BID (20.2% versus 25.7%, HR 0.72, 95% CI 0.58–0.88, $p < 0.001$) or dabigatran 110 mg BID (15.4% versus 26.9%, HR 0.52, 95% CI 0.42–0.63, $p < 0.001$). Although the study was not sufficiently powered for the composite efficacy end point of thromboembolic events, death, or unplanned revascularization, the pooled double-therapy groups met criteria for non-inferiority to triple therapy (13.7% versus 13.4%, HR 1.04, 95% CI 0.85–1.29, $p = 0.005$).[6]

The latest trial in search of the ideal antithrombotic therapy was published in early 2019. The AUGUSTUS trial (Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) applied randomization to patients (n = 4614) with atrial fibrillation and an indication for dual antiplatelet therapy (ACS or PCI). Using a 2 × 2 factorial design, the trial examined 2 hypotheses, one related to the safety and efficacy of warfarin compared with apixaban and the other related to the safety and efficacy of low-dose ASA compared with placebo.[7] All patients received a P2Y12 inhibitor. Randomization had to occur within 14 days of ACS or PCI. This trial demonstrated that triple therapy with either warfarin or apixaban was linked to higher rates of bleeding than was the case with dual therapy (16.1% versus 9.0%,

HR 1.90, 95% CI 1.59–2.24, $p < 0.001$). Lower rates of bleeding (major or clinically relevant non-major) were seen in the apixaban group than in the warfarin group (10.5% versus 14.7%, HR 0.69, 95% CI 0.58–0.81, $p < 0.001$). As with the previous trials, AUGUSTUS was not sufficiently powered to evaluate efficacy outcomes. However, the incidence of death or hospital admission was lower among patients taking apixaban than among those taking warfarin, and the incidence of death, hospital admission, and ischemic events was similar among patients receiving double versus triple therapy.[7]

A network meta-analysis, which analyzed the WOEST, RE-DUAL, PIONEER-PCI-AF, and AUGUSTUS trials and which pooled 10 026 patients for analysis, has now been published, and it begins to address the power concerns with the individual trials.[8] Its conclusion re-emphasized that omitting ASA lowers the rate of major bleeding without a significant change in major adverse cardiac events, relative to triple-therapy regimens.[8] We acknowledge that there are limitations to the trials discussed, especially the fact that all trials used safety as a primary end point, and we also acknowledge that they were underpowered with respect to efficacy outcomes of cardiovascular death, myocardial infarction, and stent thrombosis. However, it is unlikely that there will ever be a randomized controlled trial with a primary efficacy outcome, given sample size requirements of at least 20 000 participants. In addition, although we have been using the term "double therapy", patients in these studies received triple therapy for some time before randomization (up to 3 days in the PIONEER-AF PCI trial, up to 5 days in the RE-DUAL trial, and up to 14 days in the AUGUSTUS trial).[5-7] Finally, physicians recruiting patients for these trials may not have approached individuals with high thrombotic risk (such as left main artery stenting or high thrombotic burden) to discuss study involvement. Such selective recruitment, a common problem in trials, would limit the generalizability of study findings to those with low to moderate thrombotic risk.

With the evidence available today, triple therapy as a blanket approach for all patients leads to an unnecessarily high rate of bleeding with no obvious benefit with respect to efficacy. For the population at large, available evidence points clinicians to double therapy, with traditional triple therapy being reserved for the outliers of the population who are at above-normal risk of thrombotic complications.

References

1. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J*. 2009;30(9):1038-45.
2. Kralev S, Schneider K, Lang S, Suselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PloS One*. 2011;6(9):e24964.
3. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170(16):1433-41.
4. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-15.
5. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375(25):2423-34.
6. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-24.
7. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-24.
8. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol*. 2019;4(8):747-55.

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THE "CON" SIDE

Dual antiplatelet therapy, consisting of acetylsalicylic acid (ASA) with a P2Y12 antagonist, is required after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) to prevent stent thrombosis and myocardial infarction. A common scenario arises when a patient needs dual antiplatelet therapy after PCI and also oral anticoagulation for atrial fibrillation. The use of dual antiplatelet therapy plus oral anticoagulation (known as triple therapy) carries concerns about increased risk of hemorrhage. Thus, clinicians are faced with a dilemma: either treat post-PCI patients who have atrial fibrillation with triple therapy to reduce the risk of cardioembolic and ischemic events, with acceptance of a higher risk of bleeding, or reduce the antithrombotic regimen to minimize the risk of bleeding, with acceptance of the possibility of more ischemic events. Both bleeding and cardiovascular events (stroke, stent thrombosis, myocardial infarction) are associated with poor outcomes.[1]

In recent years, a flurry of large trials have been published that attempt to provide guidance in this clinical dilemma. The WOEST trial was the first study to investigate triple therapy versus double therapy consisting of clopidogrel plus warfarin[2] (Table 1). Subsequent trials—PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS—compared use of a P2Y12 antagonist plus direct oral anticoagulant with triple therapy.[3-5] On the basis of these trials, the approach of omitting ASA and instead using only a P2Y12 antagonist (mainly clopidogrel) plus oral anticoagulant (i.e., double therapy) for post-PCI patients who have atrial fibrillation has been rapidly adopted. However, a review of the evidence, as outlined below, indicates that we should not universally omit ASA and employ double therapy for all post-PCI patients with atrial fibrillation.

Trials of Double Therapy Were Safety Trials with Major Bleeding as a Primary End Point

Foremost, the trials evaluating double therapy (WOEST, PIONEER AF-PCI, RE-DUAL, AUGUSTUS) were designed as safety trials. As such, the incidence of bleeding was the primary end point for the comparison between triple therapy and double therapy; cardiovascular outcomes were secondary composite end points. In all of these trials, bleeding was significantly lower in patients treated with double therapy than among those treated with triple therapy. Thus, the trials demonstrated the intuitive conclusion that the less antithrombotic therapy a patient receives, the lower the patient's risk of bleeding. Although there was no difference in stent thrombosis or myocardial infarction between the 2 groups across these trials, the trials were underpowered to detect such cardiovascular end points. The authors of the PIONEER AF-PCI trial (n = 2124) estimated that a study to establish superiority of clopidogrel plus rivaroxaban over triple therapy in terms of myocardial infarction would require more than 40 000 patients.[3] The RE-DUAL trial was originally designed to enrol 8520 patients to allow for evaluation of an efficacy end point of thrombotic events, but because of feasibility issues, only 2725 patients were recruited, leaving it underpowered.[4] The AUGUSTUS trial,[5] which evaluated clopidogrel plus oral anticoagulant versus ASA plus clopidogrel plus oral anticoagulant, demonstrated lower rates of major or clinically relevant non-major bleeding in the double-therapy group and no statistical difference in the rates of ischemic events. However, the statistical framework for AUGUSTUS, including sample size calculation, was designed for comparing apixaban and warfarin, not for comparing ASA and placebo.[6] Of concern, the authors of the AUGUSTUS study noted a greater number of coronary ischemic events among patients who did not take ASA relative to those who did take ASA (ASA versus placebo, hazard ratio [HR] for death or ischemic event 0.89, 95% confidence interval [CI] 0.71–1.11; HR for myocardial infarction 0.81, 95% CI 0.59–1.12; HR for stent thrombosis 0.52, 95% CI 0.25–1.08). Although this observation was not statistically significant, the authors stated that it should be considered exploratory and noted that a similar pattern of more coronary ischemic events with omission of ASA had been observed in similar trials.[5] Thus, the conclusion from these often-quoted trials is that omitting ASA and using double therapy leads to less major bleeding. However, we cannot definitively state that the rates of ischemic events are unchanged with double therapy, given that all of the trials were underpowered to detect these important clinical events, heterogeneity existed among the trials, and the studies included mainly patients with lower ischemic risk.

Dual Antiplatelet Therapy Has Decades of Highest-Level Evidence

Dual antiplatelet therapy after PCI is supported by decades of literature and the highest level of evidence.[7,8] There is also robust evidence showing superior reduction in ischemic events with longer-term dual antiplatelet therapy after PCI (the PEGASUS trial).[9,10]

The use of warfarin or direct oral anticoagulant provides little benefit in post-PCI patients in terms of preventing stent thrombosis or recurrent myocardial infarction.[11] In fact, there was

Table 1. Summary of Major Trials* Comparing Triple Therapy and Double Therapy

WOEST[2]				PIONEER-AF[3]				RE-DUAL[4]				AUGUSTUS[5]			
Study population: patients with AF, after PCI (n = 573) Indication for PCI: ACS (25%), other (75%)				Study population: patients with AF, after PCI (n = 2124) Indication for PCI: unstable angina (23.7%), NSTEMI (17.8%), STEMI (10.7%), other (52.2%)				Study population: patients with AF, after PCI (n = 2725) Indication for PCI: stable angina (41.9%), ACS (51.2%), staged procedure (18.1%)				Study population: patients with AF, after PCI (n = 4614) Indication for PCI: ACS (37.8%), medically managed ACS (23.9%), elective PCI (38.3%)			
Double therapy (warfarin plus clopidogrel) versus triple therapy				Double therapy (rivaroxaban 15 mg daily plus clopidogrel) versus triple therapy (third arm of rivaroxaban 2.5 mg twice daily plus DAPT not shown in this table)				Double therapy (dabigatran 150 mg or 110 mg twice daily plus clopidogrel) versus triple therapy				Double therapy (clopidogrel plus OAC) versus triple therapy (ASA plus clopidogrel plus OAC) (2 × 2 study; apixaban versus warfarin cohort not included in this table)			
Outcome	**Double**	**Triple**	***p* Value**	**Outcome**	**Double**	**Triple**	***p* Value**	**Outcome**	**Double***	**Triple**	***p* Value**	**Outcome**	**Double**	**Triple**	***p* Value**
Primary: Any bleeding within 1 year of PCI	19.4%	44.4%	<0.0001	Primary: Clinically significant bleeding or bleeding requiring medical attention	16.8%	26.7%	<0.001	Primary: Major or clinically relevant non-major bleeding	20.2%	26.9%	<0.001	Primary: Major or clinically relevant non-major bleeding	9%	16.1%	< 0.001
Secondary: Death, MI, stroke, target vessel revascularization, stent thrombosis	11.1%	17.6%	0.025	Secondary: Death from cardiovascular causes, MI, or stroke	6.5%	6%	NS	Secondary: Thromboembolic event, death or unplanned revascularization	13.7%	13.4%	0.005 for non-inferiority	Secondary: Death or ischemic event	7.3%	6.5%	Not tested

ACS = acute coronary syndrome, AF = atrial fibrillation, ASA = acetylsalicylic acid, DAPT = dual antiplatelet therapy, MI = myocardial infarction, NS = not significant, NSTEMI = non-ST elevation myocardial infarction, OAC = oral anticoagulant, PCI = percutaneous coronary intervention, STEMI = ST elevation myocardial infarction.
*Dabigatran 150 mg bid.

a signal within the RE-LY trial that dabigatran might actually increase rates of myocardial infarction.[12] However, re-analysis of data from RE-LY and subsequent trials did not replicate this finding, and it has now been established that use of direct oral anticoagulant does not influence rates of coronary ischemic events.[13,14] Thus, we can conclude that oral anticoagulant does not contribute to reducing stent thrombosis or myocardial infarction; however, dual antiplatelet therapy is well proven in preventing these coronary events. We should not be distracted by recent trials of double therapy to forget the vast amount of prior evidence supporting the critical role of ASA as part of dual antiplatelet therapy in the context of triple therapy.

International Cardiology Guidelines Still Endorse Triple Therapy after PCI in Patients with Atrial Fibrillation

Canadian, US, and European guidelines all advocate that the choice between triple therapy and double therapy should be based on the balance between thrombotic risk and bleeding risk for each patient.[15-17] If the patient's thrombotic risk is high and bleeding risk is low, then triple therapy is recommended. If the patient's thrombotic risk is low and bleeding risk is high, then double therapy should be considered. The most recent Canadian Cardiovascular Society guidelines on antiplatelet therapy state that the timing of discontinuation of ASA will vary depending on the individual patient's ischemic and bleeding risk.[15] The duration of triple therapy can be individualized, but ASA as part of dual antiplatelet therapy in the context of triple therapy has a prominent role in the first months after stent insertion and in high-risk patients.

Conclusion

Omitting ASA and using double therapy in patients with atrial fibrillation after PCI should not be the default regimen. The decision to continue or discontinue ASA should be based on assessment of the individual patient's thrombotic and bleeding risk. The quantity and quality of evidence supporting use of ASA as part of dual antiplatelet therapy in the context of triple therapy to reduce coronary events, particularly in patients with high ischemic risk and low bleeding risk, outweighs the evidence for double therapy.

References

1. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Baadimon L, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J*. 2011;32(15):1854-64.
2. Dewilde JW, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet.* 2013;381(9872):1107-15.
3. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med.* 2016;375(25):2423-34.
4. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-24.
5. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380(16):1509-24.
6. Lopes RD, Vora AN, Liaw D, Granger CB, Darius H, Goodman SG, et al. An open-label, 2×2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS trial. *Am Heart J.* 2018;200:17-23.
7. Chua D, Ignaszewski A. Clopidogrel in acute coronary syndromes. *BMJ*. 2009;338:b1180.
8. Chua D, Nishi C. New antiplatelet agents for cardiovascular disease. *CMAJ*. 2013;185(16):1405-11.
9. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Streg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155-66.
10. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-800.
11. Leon MB, Balm DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic drug regimens after coronary artery stenting. *N Engl J Med*. 1998;339(23):1665-71.
12. Cairns JA, Connolly S, McMurty S, Stephenson M, Talajic M; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol.* 2011;27(1):74-90.
13. Hohnloser SH, Eikleboom JW. Direct oral anticoagulants and myocardial infarction: the dust is settling. *J Am Coll Cardiol.* 2018;72(1):27-8.
14. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012:28(2):125-36.
15. Metha SR, Bainey KR, Cantor WJ, Lordkipanidze M, Marquis-Gravel G, Robinson SD, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol*. 2018;34(3):214-33.
16. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACST). *Eur Heart J*. 2018;39(3):213-60.
17. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol.* 2019;74(1):104-32.

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Osons la différence

par Tania Mysak

Quand ce numéro sera publié, le conseil d'administration de la Société canadienne des pharmaciens d'hôpitaux (SCPH), les présidents des sections et les présidents des conseils d'administration affiliés auront terminé une séance de planification stratégique. Si vous avez déjà participé à une planification stratégique, peut-être éprouvez-vous des sentiments partagés à l'égard de cette expérience. Vous aimez l'énergie qui consiste à viser les étoiles en créant des occasions faisant progresser votre organisation. Vous détestez forger des énoncés et des objectifs idéalistes qui obligent à des actions concrètes et mesurables privées de l'étincelle de l'inspiration. Un plan stratégique bien conçu doit imprégner toute l'organisation; tout le monde doit ramer dans la même direction pour atteindre un objectif commun. Quand la haute direction articule un travail progressif en vue d'atteindre des objectifs, il est trop fréquent de voir les membres de première ligne qui ne savent pas articuler le plan, ce qui démontre une rupture du degré d'engagement et du sens de l'objectif commun. Étant donné ces limites actuelles, la SCPH ne peut pas maintenir le statu quo en matière de planification stratégique.

Conscients des changements importants à apporter au sein de la SCPH pour soutenir l'organisation, nous avons décidé d'aborder notre séance de planification stratégique un peu différemment. Nous définissons généralement une, vision et un énoncé de mission, puis nous réfléchissons à des objectifs et nous développons des stratégies ou des tactiques pour les atteindre. Mais que faire si on expose déjà le travail véritablement crucial qui s'annonce alors que l'ancienne vision et l'ancienne mission résonnent encore largement dans l'esprit des membres ?

En tant que Société, nos responsabilités fondamentales visent à articuler une mission et une vision qui trouvent un écho chez les membres et qui permettent d'exercer une gouvernance efficace tout en assurant une infrastructure qui soutienne notre travail. Dans notre dernier sondage mené auprès des membres, 84 % d'entre eux convenaient (ou étaient fortement d'accord) que nos énoncés de mission et de vision actuels devaient évoluer. Concernant la gouvernance et l'infrastructure, ce travail a été approuvé dans le plan Stratégie en vue de la pérennisation (Strategy Towards Sustainability; https://www.cshp.ca/strategy-towards-sustainability) et il incombe au chef de la direction et au personnel.

Notre activité principale se reflète dans les rôles pour lesquels nous sommes reconnus, mais aussi dans ceux que les membres jugent appropriés de la part de la SCPH. Répétons-le, notre conseil d'administration a dégagé un consensus validé par le sondage mené auprès des membres, voulant que la formation, la pratique et les normes professionnelles, la défense des intérêts, le *Journal canadien de la pharmacie hospitalière* et les services aux membres constituent l'essence même de la SCPH. Avoir de solides fondations et focaliser notre travail sur ces activités centrales nous permettent d'offrir de la valeur aux membres et de répondre aux besoins qu'ils ont exprimés.

Enfin, ayant jeté des bases solides tout en restant concentrés sur les éléments vraiment importants pour la SCPH, nous pouvons nous pencher sur les stratégies qui soutiendront l'organisation et permettront de la développer dans les années à venir. Ce sont ces « grandes idées » qui permettront à la SCPH de passer à l'étape suivante et de poursuivre sa progression, selon les discussions qui se sont déroulées dans le cadre du conseil d'administration au moment de l'élaboration du plan Stratégie en vue de la pérennisation (Strategy Towards Sustainability), lequel se concentre sur l'adhésion des techniciens en pharmacie, la spécialisation et le changement de nom de la Société. Nous avons testé ces idées dans le sondage mené auprès des membres. Notre séance de planification stratégique a été l'occasion d'approfondir ces idées et de réfléchir à la manière de faire évoluer la SCPH vers un objectif d'adhésion et de durabilité financière.

Nous vous ferons part des résultats de notre séance au cours des mois à venir et nous nous réjouissons de recevoir vos commentaires pour savoir si notre approche « différente » de cette année est la bonne !

[Traduction par l'éditeur]

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

Daring To Be Different

Tania Mysak

When this issue goes to publication, the Canadian Society of Hospital Pharmacists (CSHP) Board, Branch Presidents, and Affiliated Board Chairs will have completed a strategic planning session. If you have been part of strategic planning you may have mixed feelings on the experience. You love the energy of shooting for the stars with opportunities to move your organization forward. You hate drilling idealistic statements and goals into concrete measurable actions that lose the spark of inspiration. Done well, a strategic plan should permeate the organization: all oars rowing together to achieve a common goal. Too often, while senior leadership can articulate ongoing work toward goals, front-line members are unable to articulate the plan at all, demonstrating a disconnection in the level of engagement and sense of shared goals. Given these limitations, at this moment for CSHP, status quo strategic planning was not an option.

Recognizing the major shifts within CSHP required to sustain our organization, we made the decision to approach our strategic planning session a bit differently. Often, we develop a vision and mission statement, brainstorm goals, and then develop strategies or tactics to achieve those goals. But what if your vision and mission still largely resonate with your membership and the really critical work ahead of you is already laid out?

As a Society, our foundational responsibilities lie in articulating a mission and vision that resonate with members, having effective governance, and ensuring our infrastructure supports our work. In our recent membership survey, 84% of members either agreed or strongly agreed that our existing Mission and Vision statements should carry forward. Regarding governance and infrastructure, this work was approved in the Strategy Towards Sustainability plan (https://www.cshp.ca/strategy-towards-sustainability) and is the responsibility of the CEO and staff.

Our core business as a Society is reflected in the roles we are known for, as well as the ones members feel are appropriate for CSHP. Again, we have general consensus from our Board, validated by the membership survey, that education, professional practice and standards, advocacy, the *Canadian Journal of Hospital Pharmacy*, and member services constitute the "what" of CSHP. Having a strong foundation and focusing our work on those core business areas allows us to provide value for members and meet their expressed needs.

Finally, having laid a solid foundation and remaining focused on the pieces that really matter to CSHP, we can look at the strategies that will sustain and grow our organization for years to come. These are the "big ideas" to take CSHP to the next level and beyond discussed by the Board when developing the Strategy Towards Sustainability, centred on pharmacy technician membership, specialization, and a name change for the Society. We tested these ideas through our membership survey, and our strategic planning session was an opportunity to further discuss these ideas and consider how to move CSHP forward toward a goal of membership and financial sustainability.

We will be sharing the results of our session over the coming months and look forward to receiving feedback as to whether or not our "different" approach this year got it right!

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

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- proposent des occasions supplémentaires aux membres d'agir à titre de leaders d'opinion et de ressources clés pour le Conseil de la SCPH sur des questions de pratique spécialisée, dont la rédaction de déclarations de principes, de lignes directrices et des documents d'information pertinents

La participation aux RSP est gratuite pour les membres de la SCPH.

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