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UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

PATIENT SAFETY & QUALITY IMPROVEMENT

NEWS

The Future of Dialysis Treatment: Wearable Artificial Kidneys (WAKs)

REVIEW & CLINICAL PRACTICE

Triple Negative Breast Cancer: A Review of Common Therapeutic Targets and Current Treatment Options

COMMENTARY

Consequences of Missing Clinical Trial Data and Current Solutions

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ABOUT US

UOJM is an international, peer-reviewed journal led and published by the students of the Faculty of Medicine. We welcome submissions in a variety of areas in biomedical research and feature original research, reviews, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French, and represent the only student-run bilingual medical journal in Canada.

Le JMUO est un journal revu, édité et publié par les étudiants de la Faculté de médecine. Nous encourageons les soumissions d'une variété de différents domaines en recherche biomédicale et publions des articles de recherche originale, des articles de revue, des nouvelles et commentaires, des rapports de cas et des pièces d'opinion. Nos articles sont écrits en français et en anglais et représentent le seul journal médical bilingue géré par les étudiants au Canada.

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Address:
University of Ottawa Journal of Medicine
Journal médical de l'Université d'Ottawa
c/o UGME Room 2046
Roger Guindon Hall
451 Smyth Rd.
Ottawa, ON K1H 8M5
Canada

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Journal médical de l'Université d'Ottawa
c/o UGME Room 2046
Roger Guindon Hall
451 Smyth Rd.
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UOJM: Preface

Now in its seventh instalment, the University of Ottawa Journal of Medicine (UOJM) is en route to another successful year. To advance our goal of reaching medical and graduate students nationally, we established connections with other Canadian medical faculties with our new external team members. Indeed, we are seeing higher numbers of submissions from authors outside of the University of Ottawa. We have also continued our presence at the Ontario Medical Students' Weekend (OMSW) in the Fall, promoting UOJM and the broader discussion of basic and clinical research. In addition to this, UOJM has created several new initiatives this year including a biweekly newsletter with updates about events and topical news articles, a brand new website, an online publication-only website section, and release events where invited authors discuss their articles and how they fit into the broader scope of today's most pressing healthcare issues.

We kicked off the year with training seminars for our incoming team, including in-person training for Ottawa locals and online video training for our external team members. We have also been hosting seminars throughout the year, including training in peer review, information about predatory journals, and a talk on patient safety and blood transfusions. In addition, we have featured an impact factor talk and a Careers in Medicine three-part series with Respirologist and Scientist Dr. Dao Nguyen, Assistant Professor and Canada Research Chair in Molecular Virology and Antiviral Therapeutics Dr. Marceline Côté, and co-founder and CEO of Spartan Bioscience Dr. Paul Lem.

UOJM Issue 7.1 on Patient Safety and Quality Improvement focuses on bench to bedside advances in quality improvement and patient safety in Canadian healthcare. There are several exciting studies that aim to improve treatment safety and efficacy, as well as evaluate health threats (prevention and control) and quality improvement of current practices. The results of these studies impact different areas of healthcare, including Canadian policy, health system design, medical education, medical technology, patient programs and education, and access to healthcare and healthcare resources. The articles in this issue focus on technological improvements in healthcare, the benefits of formal coaching in the face of a cancer diagnosis, and improving quality and safety with proper training, reviews and analysis. There are also several commentaries, including a piece on the consequences of not sharing all clinical trial data.

Looking towards the next year, we anticipate continued growth and collaboration. We are proud to announce that our Fall 2017 issue will focus on **Women's Health**. The landscape of women's health is an ever-changing one and has seen a continuous stream of changes and advancements over the years. The upcoming issue has the purpose of addressing the challenges of providing optimal health care for women throughout their life, and exploring advancements in diagnostic procedures, therapeutic protocols for the management of diseases, and innovative research in gender-based biology that impacts care and treatment.

The submission deadline is September 30, 2017 at 5pm. High quality writing will be recognized with an Honorarium Award. Submissions can be made via our online submission system via this link: https://uottawa.scholarsportal.info/ojs/index.php/uojm-jmuo/about/submissions

We hope you enjoy UOJM's Patient Safety and Quality Improvement issue!

Editors-in-Chief
Laura Forrest
Ryma Ihaddadene

JMUO: Préface

Poursuivant à l'heure actuelle son septième cycle, le Journal médical de l'Université d'Ottawa (JMUO) anticipe une autre année fructueuse. Pour atteindre notre objectif de rejoindre les étudiants en médecine et aux études supérieures à l'échelle nationale, nous avons établi des relations avec d'autres facultés de médecine canadiennes par l'entremise de nos nouveaux membres externes de l'équipe. Depuis lors, nous avons reçu un nombre accru de soumissions de la part d'auteurs affiliés à d'autres universités canadiennes. Nous avons également maintenu notre présence lors la fin de semaine pour les étudiants et étudiantes en médecine de l'Ontario (OMSW) en automne, pour y faire la promotion du JMUO et encourager les discussions sur la recherche fondamentale et clinique. De surcroît, le JMUO a mis sur pied plusieurs nouvelles initiatives cette année, incluant un bulletin d'information bimensuel contenant des articles d'actualité et des mises à jour sur nos événements, un tout nouveau site Web, une page Web avec des articles publiés exclusivement en ligne, et des présentations d'articles où des auteurs invités se penchent sur les enjeux les plus importants dans le domaine des soins de santé à l'heure actuelle.

Nous avons démarré l'année avec des séances de formation pour notre nouvelle équipe, incluant des formations en personne pour les membres à Ottawa et des vidéos de formation en ligne pour les membres externes de l'équipe. Nous avons également organisé des séminaires tout au long de l'année, dont des séances sur l'évaluation par les pairs, les revues prédatrices, et la sécurité des patients en ce qui concerne les transfusions sanguines. De plus, nous avons planifié une présentation sur les facteurs d'impact et une série en trois parties sur les carrières médicales mettant en vedette Dr Dao Nguyen, Dre Marceline Côté et Dr Paul Lem. Dr Dao Nguyen est pneumologue et scientifique, Dre Marceline Côté est professeure adjointe et chaire de recherche canadienne en virologie moléculaire et thérapeutique antivirale, alors que Dr Paul Lem est cofondateur et président-directeur général de Spartan Bioscience.

Le numéro 7.1 du JMUO se concentre sur les avancées allant du laboratoire jusqu'au chevet des patients, en ce qui concerne l'amélioration de la qualité et la sécurité des patients dans le contexte des soins de santé canadiens. Il existe de nombreuses études intéressantes qui cherchent à améliorer la sécurité et l'efficacité des traitements, ainsi qu'à évaluer les menaces à la santé et l'amélioration de la qualité des pratiques actuelles. Les résultats de ces études ont des répercussions sur divers aspects des soins de santé canadiens, incluant les politiques, l'élaboration du système de soins médicaux, la formation médicale, la technologie médicale, l'éducation et les programmes pour les patients, et l'accès aux soins et aux ressources de soins de santé. Ce numéro est axé sur les progrès technologiques dans le domaine de la santé, les avantages de l'encadrement formel face à un diagnostic de cancer, et l'amélioration de la qualité et de la sécurité grâce à des formations adéquates. Il comprend des revues de la littérature, des analyses et de nombreux commentaires, dont un texte sur les conséquences de ne pas partager toutes les données des essais cliniques.

L'année prochaine, nous anticipons une collaboration et une croissance continues. Nous sommes fiers d'annoncer que notre numéro de **l'automne 2017** se penchera sur **la santé des femmes**. Le domaine de la santé des femmes est en évolution constante et a connu une série de changements et d'avancées au fil des années. Le prochain numéro a pour objectif d'aborder les défis quant à l'optimisation des soins de santé des femmes tout au long de leur vie, et d'explorer les progrès au niveau des examens diagnostiques, de la gestion des soins thérapeutiques et de la recherche innovatrice sur la biologie fondée sur le sexe, qui ont un impact sur les soins et le traitement.

La date limite de soumission pour notre numéro de l'automne 2017 est le 30 septembre 2017 à 17 h. Un prix sera remis pour récompenser l'écriture de haute qualité. Les soumissions peuvent être envoyées par l'entremise de notre système de soumission électronique au lien suivant : https://uottawa.scholarsportal.info/ojs/index.php/uojm-jmuo/about/submissions

Nous espérons que le numéro du JMUO sur la sécurité des patients et l'amélioration de la qualité vous plaira !

Rédacteurs en chef
Laura Forrest
Ryma Ihaddadene

Advocating for Older Patient Safety and Meeting the Challenges of an Aging Canadian Population: An Interview with Dr. Anna Byszewski, Geriatrician at The Ottawa Hospital

Glara Gaeun Rhee, BHSc[1]; Yuan Yi (Ryan) Dong, BHSc[1]

[1] Faculty of Medicine, University of Ottawa

ABSTRACT

Dr. Anna Byszewski, MD, is a geriatrician at The Ottawa Hospital and Regional Geriatric Program of Eastern Ontario. She completed medical school and residency training in Internal Medicine and Geriatric Medicine at the University of Ottawa. She is currently a full-time professor at the Faculty of Medicine at the University of Ottawa, an investigator at the Ottawa Hospital Research Institute, and is actively involved in developing and teaching communication, collaboration skills, and professionalism in the medical curriculum. Her remarkable dedication to improve the quality of care for geriatric patients through her teaching and practice were recognized in 2011 by The Ottawa Hospital Compass Award. As chair of a task group for the Dementia Network of Ottawa, she also produced the Driving and Dementia Toolkit that aims to improve quality of care and safety of geriatric patients with dementia behind the wheel. Her work is now an internationally recognized resource manual for health care workers, patients, and caregivers. In this interview, Dr. Byszewski highlights the important issues in improving the quality of care and safety for geriatric patients. This topic is of special importance due to the aging Canadian population and the unique challenges faced by health care providers such as reducing the risks of falls, cognitive decline, and polypharmacy.

RÉSUMÉ

Dre Anna Byszewski, MD, est une des gériatres principales à l'Hôpital d'Ottawa et au Programme gériatrique régional de l'est de l'Ontario. Elle a complété sa résidence en médecine interne et en médecine gériatrique à l'Université d'Ottawa. À l'heure actuelle, elle est professeure à temps plein à la Faculté de Médecine de l'Université d'Ottawa, chercheuse à l'Institut de recherche de l'Hôpital d'Ottawa, et est activement impliquée dans le développement et l'enseignement de la communication, des compétences de collaboration et du professionnalisme au niveau du curriculum médical. Son remarquable dévouement à l'amélioration de la qualité des soins pour les patients gériatriques, à travers son enseignement et sa pratique médicale, a été récompensé en 2011 par le Prix Compass de l'Hôpital d'Ottawa. En tant que présidente d'un groupe de travail du Réseau de la démence d'Ottawa, elle a également mis au point la Trousse d'information sur la conduite automobile et la démence, qui cherche à améliorer la qualité des soins et la sécurité au volant des patients gériatriques avec la démence. Son travail constitue désormais un manuel de ressources reconnu au niveau international, pour aider les travailleurs de la santé, les patients et les soignants qui gèrent de tels défis. Dans cette entrevue, Dre Byszewski met en évidence les questions importantes dans le domaine de l'amélioration de la qualité des soins et de la sécurité des patients chez les patients gériatriques. Ce sujet est d'une importance particulière en raison de la population canadienne vieillissante et des défis uniques qu'affrontent les gériatres, tels que la réduction du risque de chutes et la polypharmacie.

TELL US ABOUT YOURSELF, YOUR CAREER PATH, AND YOUR BACKGROUND IN GERIATRIC MEDICINE.

When I started my training in Internal Medicine, Geriatrics was a new and blooming sub-speciality with only about 25 to 30 years of history. I was probably the second or third trainee in Ottawa who was considering Geriatric Medicine residency training. Throughout my medical training, I knew that I really liked general medicine and I was not too keen on doing a speciality that would focus on one organ. I liked looking after the whole person, and especially elderly patients. During my training, I was quite influenced by my experiences with elderly patients and their families. I simply enjoyed listening to their rich life stories and attending to their complex medical issues. I also found that the elderly patients were very appreciative—they are all very grateful for the smallest things that you can do for them. Such experiences

Keywords: Geriatrics; Geriatric Medicine; Patient Safety; Aging

sparked my initial interest in Geriatrics and this rewarding journey. Another great aspect about Geriatrics is that you get to work with a big team of inter-professionals, which was quite novel in medicine at that time when I chose this sub-specialty.

WHAT PART OF YOUR JOB DO YOU LOVE, AND WHAT PART OF YOUR JOB DO YOU NOT NECESSARILY LIKE AS MUCH?

I believe we are very fortunate as medical professionals to have the privilege to work with diverse people, and to touch and listen to their interesting and often intimate and personal stories. As I already mentioned, I find geriatric patients to be absolutely amazing. Sometimes their situation can be challenging, the care we need to provide can be overwhelming, but we need to remember that we are here to support the patients and their families in crisis. It can also be very rewarding when you are able to resolve their issues.

The part that I like the least about my work is some of the the administrative work in the clinic; this includes paperwork and charting. As important as it is, it takes us away from patients. It's unfortunate how we have to spend up to 25% of our clinic time in front of our computers rather than with patients. I hope that there is something we can do in the future to change this pattern.

WHAT DOES "PATIENT SAFETY" MEAN TO YOU? WHAT ARE THE IMPORTANT COMPONENTS OF PATIENT SAFETY IN CARE OF THE ELDERLY?

Patient safety is about providing the best care, implementing prevention of safety risks, and avoiding errors. We identify cognitive errors and system errors. It's essentially what medicine is all about. When taking the Hippocratic Oath, we declare commitment to do no harm, non-maleficence. Many of our daily tasks could potentially threaten patient safety, including medications we prescribe and investigations we order. In the Geriatric unit, we do our best to implement many safety checks and avoid human errors whenever possible. For example, when I write my medication order, I know the pharmacist will be there to review the order and make sure I am on the right track. Another example would be consulting closely with a dietician regarding a specific diet for a patient. These safety checks are essential in Geriatrics since patients often present with very complex medical problems. There are disease-disease interactions, disease-medication interactions and medication-medication interactions. Keeping this in mind, it takes time to perform what we call a "Comprehensive Geriatric Assessment" with all these safety checks. I feel very fortunate that we have the time and resources to go through all these components very meticulously; this ensures that we are addressing patient safety in Geriatric care, each and every day.

Another quality improvement strategy includes addressing the "geriatric giants". The "geriatric giants" include falls/immobility, incontinence, malnutrition, polypharmacy and impaired memory. De-prescribing, for example, is one of the important quality improvement methods to mitigate the risks of polypharmacy. Over the years, many elderly patients accumulate medications one after another. Although there may have been a good time to prescribe it at one point in their life, sometimes they become unnecessary at a later time and may even reduce the patient's quality of life. I believe Geriatric medicine provides us with an excellent opportunity to review lists of medications and evaluate whether they are appropriate. Some other patient safety/quality projects that members of the geriatric division are involved in include pre-op detection of frailty in older patients going for non-cardiac surgery, on-going collaboration with the Transcatheter Aortic Valve Insertion committee in improved targeting of older patients for this advanced procedure and a major multi-center trial (McGill, uOttawa, uToronto, eventually Calgary, Edmonton, Vancouver) in decreasing potentially inappropriate medication in older patients admitted to Clinical Teaching Unit medicine. We are also looking forward to working with other hospital units, such as the trauma unit, to support care of the older person.

HOW HAS THE INTER-PROFESSIONAL NATURE OF THE GERIATRIC DEPARTMENT AT CIVIC CAMPUS (THE OTTAWA HOSPITAL) PLAYED A ROLE IN IMPROVING GERIATRIC PATIENT SAFETY?

The inter-professionalism of our team is one of the keys to ensuring patient safety. The Ottawa Hospital has been at the forefront of encouraging inter-professionalism work and patient safety and has been recognized as a centre of excellence for this. For instance, we have introduced patient safety rounds in most divisions, including Geriatrics. During these rounds, we review cases of patients in our unit with the entire team. Specifically, we talk about the potential errors that were committed, how we could improve, and how that improvement would affect the patient's course differently. We have these rounds several times a year and follow-up actions are taken to improve our clinical practice in the future. There is also an electronic system for tracking events. In daily clinical care, we also have rounds to review cases in order to provide every patient with a complete multi-disciplinary summary. Once the patient has been with us, whether they are inpatient or outpatient, they get a package with information from different healthcare professionals. The patients often find this quite helpful and this improves compliance with recommendations.

COULD YOU TELL US ABOUT YOUR PROJECT ON THE "DRIVING CESSATION MODULE" AND HOW IT IS RELATED TO QUALITY IMPROVEMENT AND PATIENT SAFETY OF GERIATRIC PATIENTS?

The Driving Cessation Module will complement the Driving and

Dementia Toolkit, and is designed to help physicians communicate retirement from driving. This is an area in which we haven't done such a great job in society, and yet it's such an important part of dementia care. Physicians have a legal responsibility to address this. We have developed a communication module that will be available to trainees or physicians to educate them on different approaches to disclose the information with respect to driving, how to answer difficult questions, and how to deal with emotions. This module complements tools that we have already developed for physicians and families. It is certainly a very difficult conversation to have—especially when patients are losing awareness that they may not be safe to drive, but they insist that they want to drive. This accredited module will be available online.

WHAT WAS YOUR INSPIRATION TO START THE "DRIVING CESSATION MODULE" PROJECT?

The Regional Geriatric Program of Eastern Ontario, based in Ottawa has been instrumental in developing resources, with recent uptake at an international level. It also started from family physicians communicating to us that they often have great difficulty addressing driving cessation with their patients. This is certainly a challenging discussion to have, as it may destroy the patient-physician relationship. Although physicians have a legal responsibility to discuss this, to preserve the patient-physician relationship they may refer to someone else to hold that conversation. They also find difficult to fit this conversation into their already overloaded schedules, and they may not have all the tools for these specialized assessments. We initially searched for available tools and there was no module of similar depth available. Thus, we created a set of tools, including the module to help facilitate this sensitive discussion.

IN YOUR OPINION, WHAT ARE THE MAJOR CONCERNS AND CHALLENGES IN GERIATRICS PATIENT SAFETY RIGHT NOW?

The biggest challenges in my experience are time and resources. Geriatric comprehensive assessment takes time, and it is definitely a challenge to provide these assessments to all the senior patients who are in need of them. This becomes especially challenging with a limited number of geriatricians and other health professionals trained in care of the elderly to provide these kinds of services. There is often a limit to time that we have to allocate to complete medical documents. We also need to ensure that there is an equal distribution of programs, such as outreach programs for isolated senior patients in rural communities, as they may be experiencing an even greater shortfall of resources.

DO YOU HAVE ANY ADVICE FOR MEDICAL STUDENTS WHO ARE INTERESTED IN IMPROVING THE QUALITY OF CARE AND SAFETY OF GERIATRICS PATIENTS?

I hope all trainees will have an opportunity to gain some expertise in Geriatric Medicine, learn some of the principles of safety and prevention, and apply it to every patient they see on other rotations, as likely this will be the population they will be looking after, whatever they decide to do. I believe we are taking steps towards it. This would be particularly important for the tsunami of baby boomers that are coming. And remember: treat the older person with the care you would like your own grandmother or mother to receive!

FOR FURTHER INFORMATION ABOUT GERIATRIC MEDICINE, PLEASE WATCH THE FOLLOWING PODCASTS:

Course: Ontario Geriatrics Learning Centre. (2017). Geriatrics. otn.ca. Retrieved 11 March 2017, from http://geriatrics.otn.ca/#tab0

Health Care Resources | Health Care Practitioners | RGPEO. (2017). Rgpeo.com. Retrieved 10 March 2017, from http://www.rgpeo.com/en/health-care-practitioners/resources.aspx

Podcast On Geriatric Medicine. (2017). YouTube. Retrieved 20 February 2017, from https://www.youtube.com/watch?v=wu87dZOr1xk&feature=youtu.be

The Future of Dialysis Treatment: Wearable Artificial Kidneys (WAKs)

Rameez Imtiaz, MSc[1]; Tharshika Thangarasa, BSc[1]

[1] Faculty of Medicine, University of Ottawa

ABSTRACT

Present day limitations in conventional dialysis therapies have prompted the medical community to explore alternative options in the management of end-stage renal disease (ESRD). The wearable artificial kidney (WAK) is a portable dialysis device, worn around an individual's waist, which aims to provide ESRD patients with sustained hemodialysis. In this paper we will explore the mechanisms by which the WAK operates, as well as the evidence for its efficacy and feasibility in clinical practice.

RÉSUMÉ

Les limites actuelles des thérapies de dialyse conventionnelles ont incité la communauté médicale à explorer des options alternatives pour la prise en charge de l'insuffisance rénale chronique. Le rein artificiel portable (WAK, de l'anglais) est un appareil de dialyse portatif, porté autour de la taille d'un individu, qui vise à fournir une hémodialyse continue aux patients atteints d'insuffisance rénale terminale. Dans cet article, nous explorerons les mécanismes de fonctionnement du WAK, ainsi que les preuves de son efficacité et de sa faisabilité en pratique clinique.

INTRODUCTION

The kidneys play a vital physiological role in maintaining normal health and homeostasis of the human body [1]. They are essential for waste excretion, maintenance of electrolyte and acid-base control, synthesis of vitamin D, and regulation of blood pressure [1]. The consequences of renal insufficiency and eventual failure are devastating, as evidenced by the severely reduced life-span of dialysis patients in comparison to healthy controls [2].

The vast majority of end-stage renal disease (ESRD) patients rely on life-long maintenance dialysis. Dialysis is a process that maintains hematological stability by removing metabolic waste and excess fluid from a patient's bloodstream. In essence, it is designed to replace the hemofiltration functions of the kidneys [1,3]. However, this treatment regimen is far from ideal. Current dialysis therapies require patients to have strict limitations on dietary and fluid intake, adherence to a heavy pill burden, and require long periods of limited mobility which, over time, can result in functional limitations [4,5]. Furthermore, accumulating evidence suggests that more frequent dialysis sessions are required to provide better electrolyte control and waste excretion [6]. The limitations of conventional dialysis therapies have prompted the medical community to explore alternative options [4]. Among these recent innovations is the production of a wearable artificial kidney (WAK) by researchers from the University of California, Los Angeles.

The WAK is a miniaturized wearable kidney device which aims to provide ESRD patients with 24-hour dialysis filtration (**Figure 1**) [4]. In this paper we will explore the mechanisms by which the WAK operates, as well as the current evidence supporting its use and its future implications.

Keywords: End Stage Renal Disease (ESRD); Wearable Artificial Kidney; Hemodialysis

Figure 1: The WAK device worn around the waist [4]

Mechanisms facilitating the function of the WAK

The WAK functions as a portable miniature hemodialysis (HD) machine that can be worn as a belt around the waist. Similar to HD, the WAK is dependent on vascular access to the blood stream. This initiates the passage of blood in a countercurrent flow with the dialysate fluid, which allows for ultrafiltration through diffusion between the two fluids (**Figure 2**) [7]. Unlike traditional HD which depends on energy consumptive roller pumps to sustain the movement of the blood and dialysate fluid in a coordinated fashion, the WAK relies on small, energy-efficient dual chamber pumps [7]. These pumps are powered by lightweight batteries that prevent irritation of the skin by emitting limited amounts of heat [7].

The WAK also eliminates the requirement for large volumes of

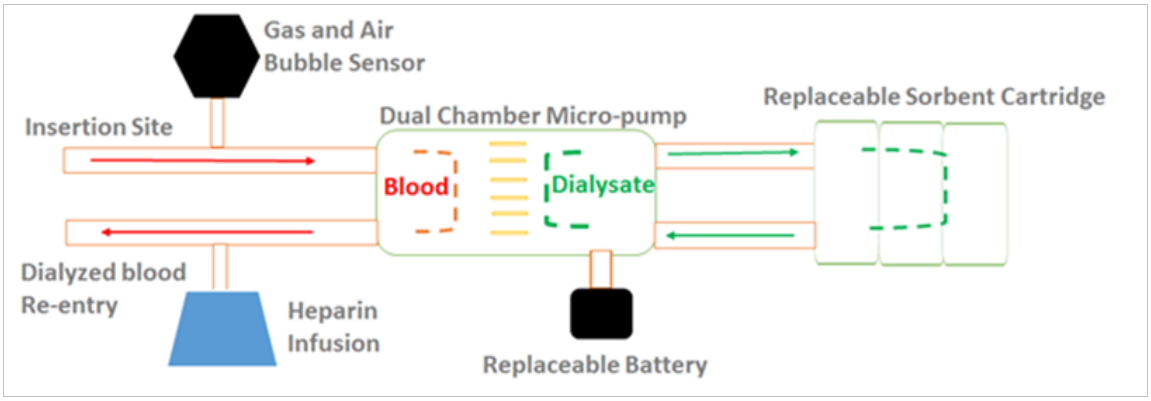

Figure 2: Simplified diagrammatic representation of the components of the WAK

dialysate fluids, which are needed in conventional dialysis to sustain filtration. The WAK is primed with a limited volume of sterile dialysate fluid which is purified by cycling through a series of microporous membranes comprised of sorbent fluids [8]. Sorbent technology consists of various particles that absorb toxins from the dialysate via diffusion across membranes, regenerating the dialysate, and allowing it to filter more blood [7-10]. The sorbent cartridges can then be disposed of at the end of the day to permanently eliminate the dangerous waste metabolites. Fresh sorbent cartridges can be reattached to the WAK to continue the purification process [7].

Furthermore, as an extracorporeal device, the WAK requires continuous access to a patient's blood stream. This can significantly elevate the risk of both blood clot and gas bubble formation [7]. To address these concerns, patients are required to be on heparin infusion, which is delivered directly by the WAK. The WAK is also equipped with a gas bubble sensor that stops blood flow if any bubbles are detected [7].

Clinical Trials of the WAK

Dr. Victor Gura, a nephrologist turned inventor, pioneered the concept of the WAK and is leading the subsequent clinical trials. Initial animal studies of the WAK, involving pigs as the test subjects, were completed in 2006 [10,11]. These studies demonstrated the WAK to be a safe alternative to conventional dialysis, with no observable side-effects [10,11]. This preclinical evidence paved the way for the first pilot study involving the use of the WAK in humans, which was published in 2007 [4]. The study involved eight patients ranging from 26-67 years of age. Patients were on the device for 4-8 hours (6.4 hours on average) and were allowed to consume food and water as they normally would [4]. The results of the pilot study in humans were promising. Body weight was significantly lower following WAK treatment suggesting that fluids could be successfully removed. Although blood and dialysate flow was lower with the WAK treatment than what is seen in conventional treatment, the WAK allows for extended continuous treatment which could produce clearance rates that exceed that of conventional treatment in the long-term. In addition, the WAK treatment did not cause any adverse changes in patients' blood electrolyte levels and blood pH remained stable [4]. This pilot study also identified several challenges. Among these, bubbles of carbon dioxide in the dialysate solution created difficulties with blood flow which could potentially attenuate embolism formation. Also, two patients experienced clotting in their access lines suggesting that anticoagulation would be an essential supplement to using the WAK [4].

Following modifications to the original design, another trial was conducted in 2016 with 7 patients (aged 27-73) undergoing WAK treatment over a 24-hour duration [4]. Given that clearance rates of solutes can vary in proportion to blood flow, the flow rate in this study was set lower to minimize fluctuations of blood solute concentrations [4]. The lower flow rate presented certain challenges. Limited clearance of a middle-molecular weight solute β2-microglobulin was observed, signifying that other middle-molecular weight molecules could also be clearing ineffectively. In addition, a rise in the phosphate levels of some patients was noted. This is of importance because hyperphosphatemia is a marker of poor prognosis in ESRD patients [12]. Regardless, patients reported overall higher levels of treatment satisfaction and no major adverse events were reported.

CONCLUSION

The current limitations of conventional dialysis have led researchers to explore alternative renal replacement therapies. Among these, the WAK has emerged as the frontrunner. Its performance in clinical trials supports its capabilities of providing successful filtration, while effectively clearing toxins [1]. However, we feel that there are still several issues that need to be addressed.

These include: determining appropriate flow rates, preventing carbon dioxide bubble formation, defining the most appropriate dosage of anticoagulant, examining the long-term safety and efficacy, and evaluating patient satisfaction after prolonged use. Future clinical trials with a larger number of patients are needed. Finally, researchers must also be wary of issues relating to costs, reimbursements, and other regulations that may accompany the usage of the WAK initially. For these reasons, we feel it is presently premature to consider incorporating the WAK into clinical practice. However, when further clinical trails to better characterize the capabilities of the WAK have been completed, it could prove to be an intriguing option for ESRD patients, improving their quality of life and possibly their prognosis.

REFERENCES

1. Fissell WH, Shuvo R. The Implantable Artificial Kidney. Semin Dial. 2009;22(6):665-70.
2. Saran R, Li Y, Robinson B, et al. USRDS 2014 annual data report: atlas of end-stage renal disease in the United States. Renal Data System. 2014.
3. Abouna GM. Organ shortage crisis: problems and possible solutions. Transplant Proc. 2008;40(1):34-8.
4. Gura V, Matthew RB, Bieber S, et al. A wearable artificial kidney for patients with end-stage renal disease. JCI Insight. 2016;1(8):pii: e86397.
5. Chiu YW, Teitelbaum I, Misra M, De Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clin J Am Soc Nephrol. 2009;4(6):1089-96.
6. FHN Trial Group. Chertow GM, Levin NW, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010;363(24):2287-300.
7. William FH, Roy S, Davenport A. Achieving more frequent and longer dialysis for the majority: wearable dialysis and implantable artificial kidney devices. Kidney Int. 2014;84(2):256-64.
8. Gura V, Davenport A, Beizai M, Ezon C, Ronco C. β2-microglobulin and phosphate clearances using a wearable artificial kidney: a pilot study. Am J Kidney Dis. 2009;54(1):104-11.
9. Agar WMJ. Review: Understanding sorbent dialysis systems. Nephrology. 2010;15(4):406-11.
10. Gura V, Masoud B, Carlos E, Polaschegg H. Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK). Contrib Nephrol. 2005;149:325-33.
11. Gura V, Masoud B, Carlos E, Edmond R. Continuous renal replacement therapy for congestive heart failure: the wearable continuous ultrafiltration system. ASAIO J. 2006;52(1):59-61.
12. Komaba H, Fukagawa M. Phosphate-a poison for humans?Kidney Int. 2016;90(4):753-63.

Transforming Community Cancer Care: The Ottawa Regional Cancer Foundation's Cancer Coaching Practice

Linda Eagen, MBA, Founder of Cancer Coaching[1]; Johanne Levesque, BScN, RN, MPA[1]

[1] Ottawa Regional Cancer Foundation

ABSTRACT

Community services are an increasingly important part of the healthcare landscape. Services that work to empower patients and their caregivers are having a positive impact on health outcomes and helping to reduce per capita costs of healthcare. According to the 2015 Canadian Cancer Statistics Report, by 2030 the annual number of new cancer cases in Canada is expected to increase by 79% [1]. Community-based cancer services, in particular, are urgently required to meet the growing demand for care as the complexity of the disease and its treatment continues to grow.

RÉSUMÉ

Les services communautaires jouent un rôle de plus en plus important dans les soins de santé. Les services qui veillent à habiliter les patients et leurs proches aidants ont un effet positif sur les résultats en matière de santé et aident à réduire les coûts par personne des soins de santé. D'ici 2030, le nombre annuel de nouveaux cas de cancer au Canada devrait augmenter de 79 % selon le rapport Statistiques canadiennes sur le cancer 2015 [1]. Des services communautaires pour le traitement du cancer, notamment, sont requis de toute urgence afin de répondre à la demande croissante de soins, alors que la complexité de la maladie et de son traitement ne cesse de croître.

This commentary outlines how the Ottawa Regional Cancer Foundation's Cancer Coaching practice is meeting the needs of cancer patients, their families, and caregivers—and helping to reduce the costs and demands on the healthcare system.

WHAT IS CANCER COACHING?

Cancer Coaching is a person-centred, solution-focused health intervention developed by the Ottawa Regional Cancer Foundation. Cancer Coaching actively engages clients in their own care through individual and group coaching consultations with a regulated healthcare practitioner. The program uses the client's frame of reference (i.e. their experiences, definitions of health and well-being, values and preferences) as the starting point to identify health goals, and then provides navigation, education, support, practical guidance, and skills development to help the client achieve their short and long-term goals. The Cancer Coaches help clients regain a sense of autonomy, improve health outcomes, and enhance quality of life. Cancer Coaching is open to people at all stages of diagnosis and treatment and does not require a physician's referral.

Cancer Coaching, as practiced at the Ottawa Regional Cancer Foundation, is an extension of three different programs: HealthChange® Methodology, a patient-centred health service delivery methodology developed by HealthChange® Associates (Australia), the Canadian Partnership Against Cancer's guide to cancer navigation, and the International Coaching Federation's best practices and ethical standards. By working with these partner organizations, the Cancer Foundation developed a unique program that has been shown to be effective in improving health and quality of life outcomes across the health continuum. The health continuum is an integrated system of healthcare that follows a patient ensuring they have knowledge and access to the services that best meet their needs. A health continuum model offers more comprehensive patient-centred care.

The Cancer Coaching practice is modeled on the Macmillan Cancer Support program in the U.K. and the Livestrong Survivorship Centers of Excellence in the U.S. When the Cancer Foundation began developing the Cancer Coaching service in 2010, survivorship care was a relatively new concept in Canada. It began emerging following the World Health Organization's recognition of cancer as a chronic disease. In Canada, 63% of cancer patients are expected to live at least five years post-diagnosis [2]. There is currently no national network of community-based services to help people who are living with the short or long-term effects of cancer and its treatments. Cancer Coaching is designed to help all those impacted by cancer—from diagnosis, through to treatment and end-of-life care—deal with their personal changes and overcome obstacles.

The effects of cancer span all elements of a person's life—physical, emotional and practical—and can last for weeks, months, or even years after the completion of treatment. Countries such as the U.S., U.K. and Australia have demonstrated a series of posi-

Keywords: Cancer; Coaching; Health outcomes; Community Care; Empower; Caregiver; Client; Healthcare; Patient-centred; Navigation; Education

tive outcomes when health coaching is implemented, including patients having a better adherence to treatment, better coping skills, and the ability to better take care of themselves. According to the report, Motivational Interviewing in Health Care: Helping Patients Change Behavior, this type of patient-centered coaching outperforms simple advice-giving-based approaches in 80% of clinical studies [3] and has been shown to be effective for supporting better healthcare outcomes across the care continuum [4].

WHAT IS THE ROLE OF THE CANCER COACH ON A PATIENT'S HEALTHCARE TEAM?

Cancer has a lasting impact on a person's health, functioning, sense of security, well-being, and quality of life. Survivors of cancer and their families struggle with life-altering decisions and how to cope with the effects of cancer treatment.

The Cancer Foundation's Cancer Coaching practice is based on three key processes: the first focuses on building a patient-centred alliance, the second helps the patient form an intention to act, and the third helps the patient convert their intention into meaningful action.

HOW DOES CANCER COACHING IMPROVE HEALTH OUTCOMES?

Coaching activities embed patient-centered care, health literacy, self-management support, and sustained behaviour change. The six key areas of the Cancer Coaching practice include: (1) assessing the needs and resources of the patient, (2) exchanging information and providing education regarding any number of client identified needs, (3) accelerating access to services and resources, (4) helping with the interdisciplinary coordination and integration of care, (5) providing support with a focus on patient empowerment, and (6) building self-advocacy competencies that aid in identifying system barriers and solutions.

The main role of the Cancer Coach is to assist the client in bringing about change that the client holds as important for improved health and quality of life outcomes. Some clients struggle with difficult decisions about treatment options, and are faced with various opinions from their network of family, friends, and healthcare providers. Cancer Coaches do not offer medical advice or treat cancer, but they work with patients to help them wade through the options presented to them by their health team. They work together, so the patient can make informed and timely decisions and play an active role in their overall health. Cancer Coaches can also provide clients with current and reliable research information on cancer treatment and care options.

A recent client survey from the Cancer Foundation shows patients who have received Cancer Coaching were better able to cope with life, better able to keep themselves as healthy as possible, have improved quality of life and feel they are part of a connected cancer care team [5]. According to doctors, patients who have experienced coaching have increased confidence in their capacity to make and sustain health changes and, because of that, they are more likely to adhere to evidence-based treatment and referral guidelines and recommendations.

HOW DOES CANCER COACHING BENEFIT FAMILY PHYSICIANS?

Patients who are diagnosed with cancer face a unique set of challenges associated with the disease and its treatments. It is estimated that 1 in 4 cancer patients have clinical depression [6], and 30% require more information about their treatment options [7], education about their diagnosis, and encouragement to seek additional help. The study also found that 35–40% of cancer patients require specialized or professional intervention for symptom management and distress.

With increased pressures on the healthcare system, medical professionals, on average, have 15 minutes per visit to spend with their patients. Physicians who participated in a pilot project of referring patients to the Cancer Foundation's Cancer Coaching practice confirmed that after receiving individual coaching, their patients were better prepared for their medical appointments and could maximize the time with their physicians and focus on key issues. In addition, they confirmed that the patient-provider interactions were more meaningful and effective, which resulted in a more efficient use of time.

Clients who access Cancer Coaching often struggle with the following areas: dealing with stress, caregiver support, learning about resources available in the community, managing post-treatment transitions, managing and improving fatigue and grief and bereavement support. Other challenges include managing the physical, informational, emotional, and practical demands of cancer and dealing with barriers such as lack of money, social supports, difficulties with health literacy, mental and medical co-morbidities, and multicultural approaches to health.

ARE THERE PLANS TO EXPAND THE CANCER COACHING PRACTICE?

The long-term vision for the Cancer Foundation is to make Cancer Coaching available to everyone diagnosed with cancer, and to share the knowledge gained through the Cancer Coaching practice with other chronic disease areas. To reach that goal in Eastern Ontario means building the capacity to serve approximately 10,000 people at any given time. In the Champlain Local Health Integration Network (LHIN) there are an estimated

7,900 new cancer diagnosis every year [8]. The Champlain LHIN is one of fourteen community-based organizations established by the Ontario Ministry of Health and Long-Term Care to help with the integration of healthcare services at the regional level. To expand the reach of Cancer Coaching, the Cancer Foundation has partnered with a number of health care providers, including Winchester District Memorial Hospital, Hospice Care Ottawa, which is a community-based organization that provides palliative and end-of-life care, and the Vanier Community Service Centre, which is a community development organization that offers a variety of programs and services to its clientele.

The Cancer Foundation has also developed, in collaboration with York University and HealthChange® Associates (Australia), a program designed to train healthcare providers in the delivery of the Cancer Foundation's Cancer Coaching practice, in order to ensure consistency and quality of the client experience.

CONCLUSION

Cancer incidence rates are on the rise, but thanks to improved screening programs and advancement in cancer research, patients have access to earlier diagnosis and better treatment options. The result: more people are surviving the disease and experiencing an improved quality of life.

With these scientific discoveries, cancer is more widely viewed today as a chronic illness and one that can, for the majority of cases, be treated and managed. This has resulted in a significant paradigm shift in the healthcare system, moving patients away from acute care in hospital to a community-based setting.

The Ottawa Regional Cancer Foundation's Cancer Coaching practice is an innovative solution that serves as the connector for cancer care. With the use of technology and enhanced communications systems, patients can access information and make their own decisions about what is best for them. They are emerging as informed consumers of healthcare, and are taking an active approach to their own healthcare. The Cancer Coach works in collaboration with the patient, empowering them to make informed decisions about their own care and share in the decision-making process with their healthcare practitioner.

More information about the Ottawa Regional Cancer Foundation's Cancer Coaching practice can be found at www.ottawacancer.ca or by calling (613) 247-3527.

REFERENCES

1. Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada, Provincial/Territorial Cancer Registries. Special topic: Predictions of the future burden of cancer in Canada. Canadian Cancer Statistics, Chapter 7, page 95 [Internet]. May 2015. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf?la=en%20Canadian%20Cancer%20Statistics,%202015
2. Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada, Provincial/Territorial Cancer Registries. Special topic: Predictions of the future burden of cancer in Canada. Canadian Cancer Statistics, Chapter 5, page 60 [Internet]. May 2015. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf?la=en%20Canadian%20Cancer%20Statistics,%202015.
3. Rubak S, Sandboek A, Lauritzen T, Christensen B. Motivational Interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005;55(513):305-12.
4. Rollnick, S, Miller, WR, Butler CC. Motivational Interviewing in Health Care: Helping Patients Change Behavior. New York: The Guilford Press; 2008
5. Ottawa Regional Cancer Foundation. Cancer Coaching Client Feedback Survey, 2014-2015, percentages refer to survey respondents who agreed completely or somewhat to survey questions.
6. National Cancer Institute - Depression (PDQ®)–Health Professional Version, [Internet]. March 2016. Available from: https://www.cancer.gov/about-cancer/coping/feelings/depression-pdq.
7. Howell, D., Currie, S., Mayo, S. et al. A Pan-Canadian Clinical Practice Guideline: Assessment of Psychosocial Health Care Needs of the Adult Cancer Patient, Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology, May 2009.
8. Ministry of Finance (% population >50). Quick Statistics: 2016 Projected Data. March 2016. Available from: http://www.csqi.on.ca/by_lhin/champlain_lhin/. Notes: Projected new cases are based on the NCI SEER standards for counting multiple primary cancers, which were adopted by the Ontario Cancer Registry for cases diagnosed in 2010 and beyond.

PICC Your Battles: Considering the Appropriateness of Peripherally Inserted Central Catheter (PICC) Lines for Outpatient Parenteral Antimicrobial Therapy (OPAT) in Injection Drug Users (IDUs)

Maxime Jasmine Billick, BA[1]

[1] Faculty of Medicine, McGill University

ABSTRACT

Injection drug users (IDUs) requiring outpatient parenteral antibiotic therapy (OPAT) for injection-related infections are regularly denied the use of peripherally inserted central catheter (PICC) lines based on the assumption that they will use the port to inject illicit drugs, and that it will be used in a non-sterile/unclean fashion. While IDUs have higher rates of infective endocarditis, abscesses and septicemia, there is no substantial body of evidence that PICC lines in IDUs result in more serious infections, increased overdoses or increased morbidity or mortality. Successful transition of IDUs from inpatient treatment to OPAT requires appropriate patient selection. Namely, housing status, mental health history, the presence of a support system, and a patient's willingness to comply with treatment all play a significant role in OPAT success. Honest and straightforward conversations must be undertaken between patient and provider regarding the risks and benefits of a PICC line if injecting drugs. Close follow-up, a compassionate approach, provider education, and the expansion of respite programs all introduce novel spaces for ongoing harm reduction and good patient care. Finally, further research is needed to establish protocols, guidelines, screening criteria, transition of care, and to clarify best practices for OPAT in patients who inject drugs.

RÉSUMÉ

Les utilisateurs de drogues injectables (UDIs) ayant besoin d'une antibiothérapie par voie parentérale ambulatoire (APA) pour des infections associées aux injections se voient fréquemment refuser l'accès à un cathéter central à insertion périphérique (PICC, de l'anglais) puisqu'on présume qu'ils l'utiliseront pour s'injecter des drogues illicites, et que le cathéter sera utilisé de manière non stérile ou peu hygiénique. Bien que les UDIs présentent des taux plus élevés d'endocardite infectieuse, d'abcès et de septicémie, il n'existe pas de preuves substantielles qui démontrent que les PICCs chez les UDIs entraînent des infections plus sévères, ou une hausse de surdoses, de morbidité ou de mortalité. La transition réussie des UDIs d'un traitement hospitalier vers une APA exige une sélection attentive des patients. Notamment, la situation de logement, les antécédents de santé mentale, la présence d'un système de soutien et la volonté du patient de suivre le traitement contribuent tous au succès de l'APA. Des conversations honnêtes et directes doivent avoir lieu entre le patient et le fournisseur de soins quant aux risques et aux avantages d'un PICC et de l'utilisation de drogues injectables. Un suivi étroit, une approche compatissante, la formation appropriée des fournisseurs de soins, et l'expansion des programmes de répit constituent tous de nouvelles façons de réduire les méfaits et d'améliorer les soins aux patients. Finalement, plus de recherche est nécessaire afin de mettre en place des protocoles, des lignes directrices, des critères de dépistage et des transitions de soins, et pour clarifier les pratiques exemplaires quant à l'APA chez les patients qui utilisent des drogues injectables.

BT lay with her head cocked in the only comfortable position, her thin legs protruding below flimsy hospital sheets. I was on a rotation in Infectious Diseases based at several Toronto-area hospitals and she was not my first intravenous (IV) drug-using patient. She was, however, the first patient I had seen who was unable to move her head more than several millimeters in either direction since a paraspinal abscess precariously abutted her spinal cord.

BT could be argumentative—she had yelled at several nurses and often refused to have her vital signs taken. She also told me she was scared—she recognized that finding herself in this position was likely secondary to her IV drug use. Despite delivering attentive care, some of the nurses rolled their eyes when talking about BT, and the social worker said that the patient refused her entry into the hospital room because she "didn't like [her] face."

Keywords: Drug Users; PICC Placement; Abscess; Heroin Dependence; Harm Reduction

The sentiments I witnessed towards injection drug users (IDUs) are not unique to my clinical rotation. A recent meta-analysis sought to assess health professionals' attitudes regarding patients with substance use disorders and to examine the consequences on healthcare delivery [1]. The analysis revealed that health care workers generally held negative attitudes toward patients with substance use disorders, often taking an avoidant approach to healthcare provision [1]. This resulted in shorter visits, diminished empathy, and lower personal engagement, presumed to result in subpar healthcare delivery [1]. Additionally,

the negative attitudes of health professionals add a significant barrier to patient recovery, since healthcare workers often play a crucial role in recognizing substance use problems, empowering patients, and acting as gatekeepers to treatment [1].

BT required six weeks of antibiotic therapy, most of which necessitated IV delivery via a peripherally inserted central catheter (PICC) line. Numerous people on her immediate treating team including nurses, attending surgeons, residents, and other consultants were dismayed that an IDU would likely need a semi-permanent PICC line.

Tertiary care hospitals throughout Canada arrange outpatient parenteral antimicrobial therapy (OPAT) for patients requiring long-term IV antibiotic delivery. OPAT has demonstrated cost-effectiveness benefits when compared to a full in-hospital IV antibiotic treatment course [2]. A recent analysis of a 334-person cohort in the UK estimated a yearly cost of approximately £300,000 (including pre-clinical set-up costs), whereas the minimum theoretical in-patient cost was more than three times higher at £1,005,676 [3]. Hospitalizing people solely for IV antimicrobial treatment is not cost effective. Moreover, an additional bed is occupied, which could be given to a patient in need [3]. Despite this, many physicians continue to believe IDUs should not be discharged with a PICC line under any circumstances [4]. During my clinical training, common beliefs I noted among medical professionals included infection of the line itself, and that the resulting infection would inherently be more serious than one acquired by self-injection. Others surmised that the individual may use the port to inject drugs.

Fundamentally, there is no consensus in the literature that supports these statements. People who use IV drugs do have higher rates of infective endocarditis, abscesses and septicemia [5-7]. However, there is no meaningful body of evidence that PICC lines in IDUs result in more serious infections, increased overdoses, or increased morbidity and mortality. In fact, the few studies that have examined PICC line complications concluded that complication rates were similar amongst IDUs and non-users [8]. Moreover, improvement and recovery rates were high among IDUs with PICC lines (73.3% cure rate, 23.3% readmission rate, 3.3% relapse rate), and no deaths, serious misadventures or line tampering were reported [9,10].

Physicians' own discomfort with discussing IV drug use may be reflected in the paucity of patient-physician conversations. In a study conducted by the National Center on Addiction and Drug Abuse at Columbia University, less than 20% of primary care doctors described themselves as "very prepared" to identify alcoholism and illegal drug use, and over 50% of patients with substance use disorders said their primary care physician did not address their substance abuse [11]. Honest and straightforward conversations must be held between patients and providers regarding the importance of keeping the PICC line as clean as possible, given its indwelling nature and the increased risk of endocarditis in IDUs. If patients plan or believe they might use the PICC line for injecting drugs, oral antibiotic alternatives may be tried with the understanding that they may be less effective [6,8,12]. Patients can also be encouraged to inject more safely by cleaning the site adequately, using sterile water to mix with their drugs, using new needles each time, and not sharing paraphernalia [13]. Additionally, appointments with patients at one-week intervals, repeat blood tests and cultures, and close follow-up for symptoms or signs of infection is essential (Dr. Isaac Bogoch MD MPH, personal communication, October 18, 2016). Ultimately, the goal of the treatment is not to cure someone of their substance use disorder, but rather to cure their infection and act as a liaison to further care should the patient desire.

Successful transition of IDUs from inpatient treatment to OPAT has been documented in several case reports and studies, however effective transition requires careful patient selection [10,14]. Ho et al. demonstrated that patients stratified by predefined criteria can be safely and successfully treated with OPAT [10]. Patients signed a contract asserting they would comply with daily OPAT visits, they would not access the PICC line for drug injection, and they would not take drugs unless prescribed by a hospital physician [10]. Formal drug counselling was provided at the onset and as needed [10]. Intermittent IV drug use was not a definite dismissal from the program as long as the PICC line was not used [10]. PICC lines were inspected by nurses for breach of security seals (stickers) prior to antibiotic administration [10]. With these conditions in place, the investigators obtained similar rates of readmission and PICC line infections between IDUs and non-IDUs [10].

More recently, the importance of appropriate patient selection for OPAT was also highlighted by Beieler et al [14]. The investigators examined the implementation of OPAT at a medical respite facility and found that rates of adverse events with IDUs (13%) were similar to that of non-IDUs (3-10%), and the readmission rate of IDUs was comparable to current literature of non-IDUs (30% compared to 9-26%, respectively) [14]. The investigators partially attributed OPAT success to the close examination of patients' social behaviours throughout the selection process [14]. Notably, IV drug use alone may be not be reflective of future OPAT success or failure. Rather, housing status, mental health history, the presence of a support system and a patient's willingness to comply with treatment all play a significant role [14-16].

The balance between patient autonomy and physician benevolence may appear tenuous when considering candidates for OPAT who inject drugs. Nonetheless, healthcare providers must provide adequate information and support to IDUs with the capacity

to consent in order to help them to make informed decisions. Care must be tailored to the individual; some IV drug users may be appropriate and reliable candidates for OPAT, while others may not be. In addition to appropriate patient selection when considering IDUs requiring OPAT, close follow-up, a compassionate approach, provider education, and expansion of respite programs all introduce novel spaces for ongoing harm reduction and good patient care. Further research is needed to clarify best practices regarding OPAT for IDUs, and to establish screening criteria and guidelines for treatment in this population.

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REFERENCES

1. van Boekel LC, Brouwers EPM, van Weeghel J, Garretsen HFL. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: Systematic review. Drug Alcohol Depend. 2013;131(1–2):23-35.
2. Wai AO, Frighetto L, Marra CA, Chan E, Jewesson PJ. Cost analysis of an adult outpatient parenteral antibiotic therapy (OPAT) programme. A Canadian teaching hospital and Ministry of Health perspective. PharmacoEconomics. 2000;18(5):451–7.
3. Chapman ALN, Dixon S, Andrews D, Lille PJ, Bazaz R, Patchett JD. Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): a UK perspective. J Antimicrob Chemother. 2009; 64(6):1316-24.
4. Mallon WK. Is it acceptable to discharge a heroin user with an intravenous line to complete his antibiotic therapy for cellulitis at home under a nurse's supervision?: No: A home central line is too hazardous. West J Med. 2001;174(3):157.
5. Hussey HH, Katz S. Infections resulting from narcotic addiction: Report of 102 cases. Am J Med. 1950;9(2):186-93.
6. Del Giudice P. Cutaneous Complications of Intravenous Drug Abuse. Br J Dermatol. 2004;250(1):1-10.
7. Management of Common Health Problems of Drug Users. New Delhi, India. World Health Organization, Regional Office for South-East Asia; 2009. 132 p. Technicla Publication Series No. 56. Available from: http://www.who.int/hiv/topics/idu/drug_dependence/hiv_primary_care_guidelines_searo.pdf.
8. Hill A, Wai A, Marsh D, Stiver HG, Sakakibara T. Pilot assessment of Intravenous Antibiotic Therapy in a Live-in Street-based Clinic, for Infections in Intravenous Drug Users (IVDU's). Poster Presentation Abstract at IDWeek. 44th Annual Meeting of the Infectious Diseases Society of America; 2006 Oct 13. Available from: https://idsa.confex.com/idsa/2006/webprogram/Paper22373.html.
9. Papalekas E, Patel N, Neph A, Moreno D, Zervos M, Reyes KC. Outpatient Parenteral Antimicrobial Therapy (OPAT) in Intravenous Drug Users (IVDUs): Epidemiology and Outcomes. Poster Presentation Abstract at IDWeek. 52nd Annual Meeting of the Infectious Diseases Society of America; 2014 Oct 11. Available from: https://idsa.confex.com/idsa/2014/webprogram/Paper46252.html.
10. Ho J, Archuleta J, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother. 2010;65(12):2641-44.
11. Missed Opportunity: National Survey of Primary Care Physicians and Patients on Substance Abuse. New York (NY). The National Center on Addiction and Substance Abuse at Columbia University. 2000 May. 105 p. Available from: http://www.casacolumbia.org/templates/publications_reports.aspx.
12. Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. BMC Infect Dis. 2014;13(14):140.
13. Kidorf M, King VL. Expanding the Public Health Benefits of Syringe Exchange Programs. Can J Psychiat. 2008;53(8):487-95.
14. Beieler AM, Dellit TH, Chan JD, et al. Successful Implementation of Outpatient Parenteral Antimicrobial Therapy at a Medical Respite Facility for Homeless Patients. J Hosp Med. 2016;11(8):531-5.
15. Bartlett R, Brown L, Shattell M, Wright T, Lewallen L. Harm Reduction: Compassionate Care Of Persons with Addictions. Medsurg Nurs. 2013;22(6):349-58.
16. Libertin CR, Camsari UM, Hellinger WC, Schneekloth TD, Rummans TA. The cost of a recalcitrant intravenous drug user with serial cases of endocarditis: Need for guidelines to improve the continuum of care. IDCases. 2017;8:3-8.

Borderline Personality Disorder: Is Diagnosis Offering Service or Stigma?

Victoria Rose Myers, BSc[1]

[1] Faculty of Medicine, University of Ottawa

ABSTRACT

Borderline personality disorder (BPD) is a common diagnosis I encountered while on my psychiatry rotation. The stigma surrounding the diagnosis and the negative attitudes of health care professionals towards these patients raised interesting questions regarding the approach to and benefit of formal diagnosis. Through reflection, two important learning points are proposed: be aware of the stigma towards BPD patients and approach each patient with an open mind and a professional attitude, and carefully examine the context of BPD symptoms before attributing a patient's difficulties to a single diagnosis.

RÉSUMÉ

Le trouble de la personnalité limite (TPL) est un diagnostic commun que j'ai croisé au cours de mon stage en psychiatrie. La stigmatisation entourant ce diagnostic et les attitudes négatives des professionnels de la santé face à ces patients soulèvent d'intéressantes questions quant à l'avantage d'établir un diagnostic officiel et l'approche à suivre pour y arriver. À la suite de réflexions, deux éléments importants à retenir sont suggérés : être conscient de la stigmatisation envers les patients avec le TPL et approcher chaque patient avec un esprit ouvert et une attitude professionnelle, et examiner attentivement le contexte entourant les symptômes du TPL avant d'attribuer les difficultés des patients à un seul diagnostic.

One of the most common diagnoses I was exposed to on my psychiatry rotation was borderline personality disorder (BPD). While the exposure gave me insight into the components of this illness, it also left me with some uncomfortable questions to reflect on. Borderline personality disorder is an illness characterized by difficulties with interpersonal relationships, self-image, emotional lability, and impulsivity. As with all personality disorders, the pattern of difficulties is inflexible and pervasive across a variety of social and personal situations and can be traced back to early adulthood (**Figure 1**) [1]. The McLean BPD screening questionnaire is a tool used clinically to assess the presence of the DSM V criteria and make a diagnosis—this was used in all the clinical encounters I observed.

The lifetime prevalence of BPD is estimated to be up to 5.9% [2]. BPD is one of the most commonly diagnosed personality disorders and makes up 10% of psychiatric outpatients and up to 20% of psychiatric inpatients [1,3]. Management of a BPD patient in crisis can be difficult as it is thought that admission to hospital is often anti-therapeutic, as it can result in further attention seeking, acting out, and self-harm behaviour. However, it is pertinent to note that a long-term study has found that patients with BPD have a suicide rate of approximately 10% [4]. Consequently, the decision of whether to admit a suicidal patient with BPD to hospital or not is an extremely difficult one that psychiatrists and emergency room physicians face on a daily basis.

The gold standard treatment for BPD is dialectical behavioural therapy (DBT). DBT is a type of cognitive behavioural therapy

Keywords: Psychiatry; Medical student; Stigma; Borderline; Personality

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment.
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Figure 1. DSM-V Criteria for Borderline Personality Disorder

(CBT) that emphasizes the acquisition of new skills to better manage dangerous behaviours, interpersonal relationships, and emotional regulation. Several studies have supported the use of DBT in patients with BPD [5,6].

During my time spent in psychiatry, a standard psychiatric clinical interaction was as follows: the patient arrived for the consult and had already been started on an SSRI or SNRI by their family physician. Their family physician would often request a formal diagnosis and advice regarding management. In the 90-minute consultation a full history was taken. The majority of patients that were diagnosed with BPD had had tumultuous childhoods and had experienced various forms of abuse. The McLean BPD screen was often used and the psychiatrist brought up the phrase 'I hate you but don't leave me'. This is a phrase commonly associated with BPD, attempting to summarize the difficulty with emotional regulation and interpersonal relationships. Patients are often asked if they can identify with this statement as a way to explore their symptoms further. At the end of consultation, a medication review was done, and they were given a referral for DBT in the community. A consult letter was written to their family doctor giving the diagnosis of BPD. The patient's chart now permanently carried the words borderline personality disorder.

Perhaps I am simplifying the consultation, but I often wondered at the end of the 90 minutes if we were doing these patients a service by diagnosing them with a label that carries a negative connotation in both the medical and real world. I am not alone in my discomfort; several health professionals around the world have discussed stigma associated with BPD—held largely by other health professionals [7]. Stigma within the health care system against borderline personality disorder has been studied amongst different groups of health care workers. A study by Markham & Trower (2003) demonstrated that when comparing patients with BPD to patients with depression or schizophrenia, nursing staff felt that the patients with BPD were more in control of their negative behaviour and felt less sympathy and less optimism towards these patients [8]. Qualitative analyses revealed common vocabulary used by psychiatrists and emergency room physicians when describing BPD patients: 'they are manipulative', 'they are time consuming', 'they are a waste of my time', and 'I find them too difficult to deal with' [9]. There is some thought that by reacting negatively and distancing themselves from patients, health care providers are propagating the negative behaviours characteristic of BPD such as attention seeking [10]. There is early evidence that increasing health care worker education about BPD improves attitudes, but education programs specific to BPD are few and far between [11].

A patient in a follow-up appointment recently noted that the idea of having a health professional refer to her illness as a 'personality issue' was offensive. She noted that when first diagnosed, she self-stigmatized and her ability to cope worsened. The patient in question seemed to struggle in particular with the idea that her illness was part of her 'personality', making her feel as though she could not overcome her struggles. This patient had been followed over a long period of time as both an inpatient and outpatient and longitudinally fulfilled criteria for the diagnosis of BPD. Although her comments raised some questions, I feel most uncomfortable regarding those who are diagnosed on the first meeting. The diagnosis of a personality disorder requires identification of a long-term pattern of specific behaviours, which is difficult to illicit in a single session. Additionally, some of the criteria on the McLean screening form are non-specific and context dependent: feelings of emptiness, lack of identity, and relationships troubled by arguments. I struggle with the idea that it is pathologic for a young adult in their late teens to struggle with identity or with relationships.

Putting my reservations aside, I recognize that diagnosis allows patients to access community DBT. I also understand the overwhelming load of patients that community psychiatrists take on and that longitudinal follow up may not be feasible in the current medical climate. Ultimately, I have taken away important lessons for myself when I am a primary care physician, whether in the ER or a community clinic:

1. Be aware of the stigma towards BPD patients and approach each patient with an open mind and a professional attitude.
2. Carefully examine the context of BPD symptoms before attributing their difficulties to a single diagnosis.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM V). 5th ed. Washington, DC: American Psychiatric Publishing; 2013. 663 p.
2. Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008;69(4):533-45.
3. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatry. 2005;162(10):1911-8.
4. Paris J. Implications of long-term outcome research for the management of patients with borderline personality disorder. Harv Rev Psychiatry. 2002;10(6):315-23.
5. van Den Bosch LMC, Koeter MWJ, Stijnen T, Verheul R, van Den Brink W. Sustained efficacy of dialectical behaviour therapy for borderline personality disorder. Behav Res Ther. 2005;43(9):1231-41.
6. O'Connell B, Dowling M. Dialectical behaviour therapy (DBT) in the treatment of borderline personality disorder. J Psychiatr Ment Health Nurs. 2014;21:518-25.
7. Sansone RA, Sansone LA. Responses of mental health clinicians to patients with borderline personality disorder. Innov Clin Neurosci. 2013;10(5-6):39-43.
8. Markham D, Trower P. The effects of the psychiatric label 'borderline personality disorder' on nursing staff's perceptions and causal attributions for challenge behaviours. Br J Psychiatry. 2003;42:243-56.
9. Treloar AJC. A qualitative investigation of the clinical experience of working

with borderline personality disorder. NZ J Psychol. 2009;38(2):30-4.
10. Aviram RB, Brodsky BS, Stanley B. Borderline personality disorder, stigma, and treatment implications. Harv Rev Psychiatry. 2006;14(5):249-56.
11. Knaak S, Szeto ACh, Fitch K, Modgill G, Patten S. Stigma towards borderline personality disorder: effectiveness and generalizability of an anti-stigma program for healthcare providers using a pre-post randomized design. Borderline Personal Disord Emot Dysregul. 2015;2:9.

A Case for an Opt-Out Organ Donation System in Canada

Taylor Aust[1]

[1] Faculty of Medicine, Université de Montréal

ABSTRACT

This commentary supports an 'opt-out' system for organ donation in Canada. To begin, it examines the state of organ donation in our country and presents both the 'opt-in' and 'opt-out' schemes. Then, it argues in favour of implementing 'opt-out' legislation in Canada, suggesting that this system makes donation easier for families and improves the donor rate. Opinions against 'opt-out' are considered and debated. Finally, other donation systems as well as potential methods to encourage organ donation are briefly discussed.

RÉSUMÉ

Ce commentaire appuie la mise en place d'un système avec option de retrait ('opt-out' system en anglais) pour le don d'organes au Canada. Tout d'abord, ce commentaire se penche sur l'état actuel du don d'organes dans notre pays et présente à la fois le modèle à option d'adhésion ('opt in') et celui à option de retrait ('opt out'). Puis, il argumente en faveur de la mise en œuvre d'une législation qui permettrait un système avec option de retrait au Canada, suggérant que cela faciliterait le don d'organes pour les familles et améliorerait les taux de dons. Certains des arguments contre le système avec option de retrait sont examinés et démontés. Finalement, d'autres systèmes de dons, ainsi que des méthodes pouvant possiblement encourager le don d'organes, sont discutés brièvement.

INTRODUCTION

Today, due to the combination of advancements in medical science and our aging population, the topic of organ donation is very noteworthy. From paediatric cases to chronic disease, transplantation of organs has become the gold standard treatment for many patients. It can allow many to regain a good standard of living as well as avoid costly and time-consuming chronic treatment. In 2014, there were 4,500 Canadians waiting for transplants, with just over 2,300 transplants performed in the same year [1]. For the survivors, waiting times can take up to years [1]. Unfortunately, of the 48% who were non-recipients, about 300 patients died in the same year [1]. Despite its many advantages, organ donation continues to be quite an emotional topic for most of the population. This is understandable, as the topic involves death of a loved one, family, and our own mortality. This easily elicits questions of an ethical, religious, and scientific nature.

CURRENT SITUATION IN CANADA

In Canada, each province and territory is responsible for its own donor registry. Most provinces operate with a registration form that is filled out in person, on paper, or online. Some provinces, such as New Brunswick, have an option available to confirm donation when renewing a health card. Others have a combination of both systems [1,2]. With many varied systems available to Canadians, the process of registering to become an organ donor is not as easy as it seems. In efforts to manage the function of organ donation and transplantation, the provinces requested a federal agency to oversee the many different processes that exist. Today, the Safety of Human Cells and Tissues and Organs for Transplantation Regulations assist Health Canada and Canadian Blood Services in managing organ donation [1]. With Canadian donation rates just under 20 donors-per-million-population, the steps that provincial and federal governments have taken seem to be lacking [3,4]. It would be preferable to have a streamlined system in place in Canada, uniform in all provinces. Having an efficient system would potentially encourage donation and boost donor rates.

There are two popular organ donation systems currently in place around the world. To begin, there is an 'opt-in' system. For this method to work, a person who wishes to become an organ donor must register in some fashion to be put on the available donor list. Conversely, the second system is called 'opt-out'. This system operates under the assumption that the majority of the population wishes to donate and therefore a person must express a refusal or remove their name from a list if they choose not to become a donor [5]. Currently, Canada is operating under an 'opt-in'-like system [1,6]. Here, we will consider the benefits of an 'opt-out' system.

ARGUMENTS FOR AN 'OPT-OUT' SYSTEM

The main argument for an 'opt-out' system stems from the logic that since the entire population is automatically on the list, the donor rate must naturally improve and subsequently, the number of transplants. In general, this idea is thought to promote organ donation. Many studies have been dedicated to confirming this hypothesis [5,6]. However, one must be careful when com-

Keywords: Organ Donation; Opt-in; Opt-out; Presumed Consent; Canada

paring donor and transplant rates in different countries. Information is treated differently across countries and the collection of statistics can introduce bias. For example, the cause of death and cultural differences can have an impact on donor statistics [7]. Furthermore, one must consider global trends while comparing donor rate increases. Yet, even while controlling for determining factors, studies show that 'opt-out' legislation increases donor rates [5,6,8,9]. For example, the donor rate in Austria quadrupled after instituting 'opt-out' legislation. Similar regulations in Belgium doubled kidney donations [9]. In 2010, European countries with 'opt-out' systems such as Croatia, Portugal, and France had higher donation rates than 'opt-in' countries [9]. These trends continue today [3]. Along with new legislation, better transplantation infrastructure, public opinion, and family education also help increase the donor rate [5].

An 'opt-out' system also has the potential to assist families in the decision to donate. The death of a loved one is unfortunate, but the decision to donate organs is a topic that must rapidly be discussed. This choice often falls to the families. Many relatives are unaware of their deceased's wishes, having never discussed the issue. In addition, this is understandably a painful and confusing time for families and the decision is not easy. This could potentially result in a higher rate of refusal. Kennedy et al. suggest that during the discussion of organ donations, the 'opt-out' system allows families to be partially relieved of the burden of deciding [7]. The families have transitioned into a position of corroborating facts instead of pushed into making a timely decision [7]. It is easy to see how this would relieve stress and conflict during the moments following the death of the patient.

DRAWBACKS OF THE 'OPT-OUT' SYSTEM

There are many who have strong opinions against the presumed consent system. For example Fabre, professor of clinical sciences at King's College London, has been very vocal in his opinions, calling the 'opt-out' scheme "unnecessary and corrupting" [10]. This is an understandable position. As we have stated at the beginning of the article, the topic of organ donation forces us to pose many ethical questions. A common argument against 'opt-out' is the aspect of informed consent. Fabre is right in calling informed consent a corner stone of medical ethics [10]. However, informing the public can be achieved by having health care professionals explain the program during regularly scheduled appointments. Public service campaigns could also have an impact on informing the community. Saunders, lecturer in philosophy at the University of Stirling, has an interesting definition of the 'opt-out' system. He suggests that 'opt-out' and presumed consent systems are different [11]. For example, Saunders states that a presumed consent system would not be preferable because "consent is not something that can be presumed". On the other hand, by using the 'opt-out' system, those who have not withdrawn their consent have implicitly consented, and this is therefore considered to be the act of consenting and does not presume consent [11]. Furthermore, considering the 'opt-in' system currently in place, we can ask ourselves if it is right to reject the organs of someone who has failed to register. The wishes of the person who failed to register should still be taken into account. A 2015 study showed that the 'opt-out' model was preferred to the 'opt-in' model when trying to maximise the proportion of people who had their end-of-life wishes respected [9]. 73% of Canadians would donate their organs; however today, less than 20% have registered as a donor or have made other plans to donate [2,12]. In an 'opt-in' system, many Canadians will not have their wishes fulfilled because they have not registered. Similarly, these people have not consented to the discard of their organs, as it was their wish to be donors.

Moreover, there are some who speculate that an 'opt-out' system will incite a social pressure to donate and in turn diminish the attractiveness of organ donation [7]. For example, Chile enacted an 'opt-out' law in 2010 after seeing donor rates drop by 40%. The sudden pressure of this change spurred public unease and millions of opt-outs. However, surveys showed that 70% of people did not fully understand the new law [5]. We can be reasonably sure that this will not be the case in Canada. There are encouraging statistics that show the majority of the population is in favour of organ donation [2,4,12]. As mentioned above, we can see that similar legislation has been accepted in other countries [5,7,9].

To make an 'opt-out' system work, it is evident that a strong public education campaign will be necessary. This campaign would have many functions. For example, informing the public of their rights, of how to 'opt-out', and informing them of the implications of becoming a donor. Thankfully, as discussed earlier, Canada already has federal systems in place to promote this type of campaign [1].

OTHER SYSTEMS

There are other potential donor systems that are not discussed in detail in this commentary. For example, mandated consent is a system where persons of age would be required to decide if they wish to become donors [13]. There could also be other options, besides legislation that would have the potential to improve donor rates. Financial incentives for donations could be used. Xenotransplantation is an interesting alternative involving the transplant of other species organs into humans [6]. A reciprocal system, where to receive an organ you must be registered as a donor and be willing to donate, has also been discussed by authors [5]. However, these systems are not widely implemented and the literature exploring these systems is not well established. Increasing awareness and improving consent rates from families

is the best option [6]. For this reason, an 'opt-out' system would still be preferable to other systems.

CONCLUSION

In conclusion, an 'opt-out' system could be suitable for Canada. It could streamline the registration process and boost donation numbers, as shown in many other countries. Even though there are perceived shortcomings with this system, it could still lead to increased donor rates in Canada. Because the majority of Canadians wish to donate, we can be reasonably sure that this new legislation, if introduced, would be widely accepted.

REFERENCES

1. Government of Canada. Blood, Organ and Tissue Donation [Internet]. Ottawa (ON): The Government of Canada, Department of Health; 2017 [updated 2017 Jan 26; cited 2017 Feb 28]. Available from: http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/donation-contribution-eng.php.
2. Canadian Transplant Society. Register Your Consent [Internet]. Toronto (ON): The Canadian Transplant Society; 2014 [cited 2017 Feb 28]. Available from: http://www.cantransplant.ca/home/organ-and-tissue-donation-consent/.
3. European Directorate for the Quality of Medicines and HealthCare. Newsletter Transplant; International figures on donation and transplantation. 2016. Volume 21.
4. Canadian Blood Services. Organ Donation and Transplantation in Canada; System Progress Report 2006-2015. Ottawa. 2016.
5. Zúñiga-Fajuri A. Increasing organ donation by presumed consent and allocation priority: Chile. Bull World Health Organ. 2015;93:199–202.
6. Abadie A, Gay S. The impact of presumed consent legislation on cadaveric organ donation: A cross-country study. J Health Econ. 2006;25:599-620.
7. Kennedy I, Sells RA, Daar AS. et al. The case for "presumed consent" in organ donation. Lancet. 1998;341:1650–52.
8. Van Dalen HP, Henkens K. Comparing the effects of defaults in organ donation systems. Soc Sci Med. 2014;106:137-42.
9. Ugur ZB. Does Presumed Consent Save Lives? Evidence From Europe. Health Econ. 2015;24:1560–72.
10. Fabre J. Presumed consent for organ donation: a clinically unnecessary and corrupting influence in medicine and politics. Clin Med (Lond). 2014;14(6): 567–71.
11. Saunders B. Opt-out donation without presumptions. J Med Ethics. 2012;38:69-72
12. Léger Marketing. Les dons d'organes; Rapport. Montréal, Québec. March 2004.
13. Spital A. Mandated Choice : The Preferred Solution to the Organ Shortage?. Arch Intern Med. 1992;152(12):2421-4.

Lack of Clinical Trial Data Transparency and Current Solutions

Tabassom Baghai, BSc[1]

[1] Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa

ABSTRACT

An ongoing challenge in clinical research is the inaccessibility of clinical trial data, which prevents physicians from making an informed decision with regards to patient care. The U.S. Food and Drug Administration (FDA) as well as the World Health Organization (WHO) recently called for all trial data to be registered and made publically available. However, this issue is still ongoing and there are several measures currently being enforced to rectify these concerns. Potential solutions, such as regulations, campaigns, and possible consequences, for increasing transparency in clinical trial data will be discussed.

RÉSUMÉ

L'inaccessibilité des données provenant d'essais cliniques constitue un défi constant en recherche clinique, puisqu'elle empêche les médecins de prendre des décisions éclairées quant aux soins de leurs patients. Récemment, le Secrétariat américain aux produits alimentaires et pharmaceutiques (FDA) ainsi que l'Organisation mondiale de la Santé (OMS) ont demandé que toutes les données d'essais cliniques soient enregistrées et mises à la disposition du public. Toutefois, ce problème persiste et plusieurs mesures ont été mises en place pour répondre à ces préoccupations. Des solutions possibles dont des réglementations, des campagnes et des sanctions possibles pour améliorer la transparence en ce qui concerne les données d'essais cliniques seront discutées.

INTRODUCTION

Treatment of patients using drugs or devices is based on the implicit trust that physicians are making rational decisions founded upon thorough knowledge of the efficacy and safety of the treatment. Once drugs and devices are developed, they are required to undergo various trial phases to test their effects on human participants who have been deemed appropriate for the study [1]. The main objective of these trials is to identify potential benefits as well as the harmful and adverse effects of these treatments [1]. Therefore, it is imperative that these results are accessible to physicians so they may determine the best treatment options for their patients. However, a current issue in clinical research is the absence of data obtained through these trials, thus limiting the basis on which physicians make their decisions [2]. This has caused the safety of patients to be at risk and will continue doing so unless the proper steps and regulations are implemented [2].

SELECTIVE REPORTING AND PATIENT SAFETY

Selective reporting, in this setting, can be defined as the act of excluding data obtained from clinical trials [3]. This can occur due to various reasons, including results that are deemed null or negative [4], or in the case of industry-funded research, treatment that does not display the desired effects the study's sponsor had hoped for [5]. Therefore, the data obtained is revised for commercial purposes so it may appear more promising [5]. This phenomenon is known as reporting bias, where researchers are more likely to report positive data as opposed to negative data [6]. This leads the public, including health care practitioners, to be misinformed and unintentionally develop a skewed opinion of the treatment [2]. As a result, treatments become overvalued and their harmful effects become underestimated, leading patients to potentially be exposed to toxicities and adverse events in the absence of any clinical benefits [3]. Moreover, without an in-depth understanding of the treatment in question, it is impossible for physicians to make a proper comparison between various treatments [2]. Consequently, a physician may select a promising drug based on the presented data, as opposed to another drug that would have been a safer choice [2]. A well-documented example that highlights the consequences of selective reporting is rofecoxib (Vioxx), a COX-2 inhibitor [3]. The risks associated with rofecoxib were not properly represented in the trial reports, which falsely reported rofecoxib's benefits on the gastrointestinal system as greater than its risks on the cardiovascular system [7]. This resulted in 88,000 to 140,000 serious cases of heart disease in the United States alone, thus resulting in the removal of rofecoxib from the market in 2004 [8].

Furthermore, without a clear representation of clinical trial results, selective reporting could lead other investigators to conduct similar trials exposing patients to adverse effects that may have been prevented with clear communication [2]. Not only does this put more patients at harm's risk, it wastes time and money that could have been spent on alternative treatments [2].

Keywords: Clinical Trials; Patient Safety; Selective Reporting

CURRENT APPROACHES

The World Health Organization (WHO) recently issued a statement advocating for the release of all data obtained from clinical trials, including those from prior years [9]. Moreover, they have also stated that the results obtained should be submitted for publication in a journal within 12 months of study completion or made publicly accessible within 24 months of study completion [10]. The availability of this knowledge will facilitate rational decision-making that is based on the safety and efficacy of treatments while avoiding misinformation and unwarranted costs [3]. WHO's statement is in support of various policies and campaigns currently taking place, which will be thoroughly discussed below.

Trial Registration

In 2007, the Food and Drug Administration Amendments Act (FDAAA) was implemented [11]. The FDAAA required all clinical trials and collected data to be registered on ClinicalTrials.gov [11]. ClinicalTrials.gov is currently the largest clinical trial database with over 200,000 trial registrations globally [12]. However, even with an accessible registry and the implemented rule of registering clinical trials, a large number of trials are continuing to omit data [13]. The FDAAA attempted to enforce the reporting of trial results with a penalty of up to $10,000 per day if they were not reported within twelve months of completion [14]. However, disadvantages of the ruling included the focus on ongoing trials in the United States as well as neglecting to enforce the penalty [6,14]. This led to many trials, including those registered, to continue to withhold results [14]. Additionally, the FDAAA ruling excludes clinical trial results obtained prior to 2007 [15], thus limiting a relatively large volume of data of which many treatments are based on today [6].

The International Committee of Medical Journal Editors (ICMJE) is attempting to help this ongoing problem by suggesting that a plan for sharing trial data should also be included with the registration [16]. They have also implemented the rule that its journals will only publish clinical trials that have been registered prior to the start of data collection [16]. The enforcement of this rule has been inconsistent and flawed, since it primarily affects clinical trials whose goal is to be published [6].

Recently, an online tool known as TrialsTracker was developed to track registered trials that have not made their results available [17]. A study looking at trials registered between 2006 and 2014, determined that 45% of registered trials were missing data associated with their study [18]. Furthermore, among the top 100 universities and institutions that were associated with a large number of absent results, nine were identified to be Canadian [18]. Interestingly, the Ottawa Hospital Research Institute (OHRI) was ranked 99 among the institutions mentioned, with 63.8% of its trials missing results [18]. This suggests that stronger rules are required to ensure that all trial data is made available for health care practitioners and patients. Registration has been a good step towards informing the public of current clinical trials [19]. However, it is the results obtained from the trials that will help determine future decisions and outcomes of patient care and safety [19]. Not only would transparency of the results help with better decision-making, it will also help facilitate the recruitment of more patients, as patients will be better aware of studies that are being conducted [20]. In addition, transparency will aid investigators, as it will prevent the unnecessary duplications of studies [2]. Moreover, having the option to share results in a clinical trial database could help avoid reporting bias since it would allow all data to be available and not only those deemed positive [2].

AllTrials Campaign

In 2013, the AllTrials campaign began in order to improve the registration and sharing of the methods and results to the public [21]. This campaign believes that all clinical trials should be registered and results made available [21]. The AllTrials campaign has received support from a number of organizations as well as patients, physicians, and investigators around the world [21]. Thus far, they have been successful in raising awareness using petitions that they forward to health and policy regulators in various countries [21]. Having its members write to individuals involved with the regulation of clinical trials, especially Members of the Parliament in Europe and Canada, has led to the passing of laws that enforce the availability of clinical trial data [22]. Furthermore, there is an increase in the number of pharmaceutical companies that are joining the AllTrials campaign, including GlaxoSmithKline (GSK) [22]. Interestingly, GSK pleaded guilty in failing to report safety data regarding Avandia, a drug used for diabetes as well as misbranding antidepressants, Paxil and Wellbutrin, in 2012, which resulted in GSK paying $3 billion in fines [23]. Thus, joining this campaign could help them repair their public credibility.

FUTURE PLANS

Audits

Many organizations and investigators continue to avoid publishing their trial data regardless of the regulations that were implemented [19]. For this reason, it may prove useful to conduct audits of the registered trials and publically identify those who have omitted data in addition to those who have been updating their database [19]. TrialsTracker is an example of an audit tool that has identified trials whose results have not been available [17]. Further audits could potentially lead investigators and companies to be accountable and begin adhering to regulations [19]. Through these audits, health care practitioners will be able to make improved and informed decisions, as they will be aware of

credible results [19].

Data-sharing Platform

Another option is to implement a data-sharing platform that will help deliver trial data in a responsible and unbiased manner [16]. An example of such a platform is the Yale Open Data Access (YODA) Project, which first started in 2011 [16]. The YODA Project acts as an independent third party intermediary between organizations and researchers that perform clinical trials and those interested in the trial results [16]. They act to objectively evaluate the data obtained in order to provide important and crucial information about treatments that aid in patient care decisions [16]. This model system could potentially help to increase trust in the data obtained from clinical trials. Johnson & Johnson, a large healthcare company, has recently partnered with the YODA project for the release of their clinical trial data [16]. Although journal publications might not be ideal for all results obtained from clinical trials, having a platform to share and report information is a proper stepping-stone for improving patient safety.

POTENTIAL CONSEQUENCES OF MANDATORY REPORTING

As mentioned thus far, the transparency of clinical trial data has become a hot topic of discussion in healthcare. Emphasis has been on the importance and benefits of having data available in order to increase the quality of patient health and safety [2-4]. The potential benefits that could emerge from proper access and availability of clinical trial data are undeniable; however, the consequences that could arise as a result should be taken into account. One issue is that transparency of data could jeopardize patient confidentiality, as the details entailed for each patient in clinical trials could potentially expose their identities [24]. Appropriate measures for data de-identification must be taken and controlled access to the data should be implemented in order to ensure patient privacy remains intact [24].

A higher level of transparency could also put commercial confidentiality at risk, especially when it comes to the pharmaceutical industry [25]. Many companies will become wary that their trade secrets and proprietary information could be made public, thus continuing to affect their willingness to share data as it may hinder product research and development [25]. Moreover, the availability of clinical trial information may also hinder the incentive for obtaining patents for drugs when properties and effects have already been disclosed [25]. For instance, there is currently a lot of focus on developing novel uses for drugs that were initially developed and tested for a certain disease, but instead possess the potential to be an effective treatment for another disease [25]. By enforcing complete transparency of data, its use as a treatment for the other disease may no longer seem novel enough for a patent, thus discouraging researchers from developing drugs through this approach [25]. Interferon-α is an example of a drug that was initially developed for the treatment of hairy-cell leukemia [26]. It is currently used for the treatments of hepatitis C as well as metastatic melanoma, among other diseases [26].

Another aspect that should be considered is whether or not to limit access to information obtained from a clinical trial to authorized researchers only [6]. It may be beneficial for the data to be independently analyzed by other researchers, especially through the emerging data-sharing platforms, in order to gain other perspectives [6]. However, if the results fall into the wrong hands or are analyzed in an unethical manner, it could lead to the disclosure of misleading information to the public, evoking unnecessary treatments due to unwarranted health scares [6].

CONCLUSION

The inaccessibility of clinical trial data remains an ongoing concern in clinical research [2]. In many cases, this has resulted in harm or even death of patients whose treatment was based on the trial data available to physicians [3]. To solve this issue, registration of clinical trials is being implemented [12], while an international campaign, AllTrials, is calling out for the release of necessary trial data, past and present [21]. Furthermore, audits are recommended as a way to specifically identify unreliable trials [19]. Data-sharing platforms are produced to present an unbiased and responsible distribution of trial data [16]. The incorporation of publication officers in the organization is taking place at the OHRI to assist with reporting clinical trial results [18]. Their role is to direct the researchers at The Ottawa Hospital in properly preparing and submitting their results for publication [18]. Making clinical trial data more accessible must continue to be implemented as it can affect a large number of people, including patients and health care practitioners. However, its risks must also be taken into account when developing policies and approaches. It is imperative that health-related research remains focused on what is best for patients.

REFERENCES

1. Umscheid CA, Margolis DJ, Grossman CE. Key Concepts of Clinical Trials: A Narrative Review. Postgrad Med. 2011;123(5):194-204.
2. Brassington I. The ethics of reporting all the results of clinical trials. Br Med Bull. 2017;121(1)19-29.
3. Gøtzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials. 2011;12(1):249.
4. Dickersin K, Chalmers I. Recognizing, investigating and dealing with incomplete and biased reporting of clinical research: from Francis Bacon to the WHO. J R Soc Med. 2011;104(12):532-8.
5. Wynia M, Boren D. Better regulation of industry-sponsored clinical trials is long overdue. J Law Med Ethics. 2009;37(3):410-9.
6. Richardson E. Health Policy Brief: Transparency in Clinical Research [Internet]. Health Affairs. 2016 Jan 14. Available from: http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_150.pdf
7. Krumholz HM, Ross JS, Presler AH, et al. What have we learnt from Vioxx? BMJ. 2007;334(7585):120-3.
8. Madigan D, Sigelman DW, Mayer JW, et al. Under-reporting of cardio-

vascular events in the rofecoxib Alzheimer disease studies. Am Heart J. 2004;164(2):186-93.
9. Jasarevic T. WHO call for increased transparency in medical research [Internet]. Geneva: World Health Organization; 2015 Apr 14. Available from: http://www.who.int/mediacentre/news/notes/2015/medical-research-transparency/en/
10. WHO Statement on Public Disclosure of Clinical Trial Results [Internet]. World Health Organization; 2015 Apr 9. Available from: http://www.who.int/ictrp/results/reporting/en/
11. Food and Drug Administration Amendments Act of 2007 [Internet]. U.S Public Law 110-85. 2007 Sept 27. Available from: http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf
12. Trends, Charts, and Maps [Internet]. Clinicaltrials.gov, U.S. National Institutes of Health. 2016 Feb. Available from: https://clinicaltrials.gov/ct2/resources/trends
13. Jones CW, Handler L, Crowell KE, et al. Non-publication of large randomized clinical trials: cross sectional analysis. BMJ. 2013;347:f6104.
14. Miller JE, Korn D, Ross JS. Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. BMJ Open. 2015;5(11):e009758.
15. FDAAA 801 Requirements [Internet]. Clinicaltrials.gov, U.S. National Institutes of Health. 2017 Feb. Available from: https://clinicaltrials.gov/ct2/manage-recs/fdaaa
16. Krumholz, HM. The Yale Open Data Access (YODA) Project – A Mechanism for Data Sharing. N Engl J Med. 2016;375:403-5.
17. Powell-Smith A, Goldacre B. The TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions. F1000Research. 2016;5:2629.
18. Hol D. 'We've been deceived': Many clinical trial results are never published [Internet]. CBC News, Canada; 2016 Nov 24. Available from: http://www.cbc.ca/news/health/clinical-trial-results-not-published-1.3865785
19. Goldacre B. How to Get All Trials Reported: Audit, Better Data, and Individual Accountability. PLOS Medicine. 2015;12(4):e1001821.
20. Ghersi D, Clarke M, Berlin J, et al. Reporting the findings of clinical trials: a discussion paper [Internet]. Bulletin of the World Health Organization. 2008;86(6):417-96.
21. AllTrials [Internet]. London, UK. 2013 Sept. Available from: http://www.alltrials.net/find-out-more/all-trials/
22. Lane, S. AllTrials campaign and petition support greater clinical trial transparency. [Internet] Elsevier. 2014 June 23. Available from: https://www.elsevier.com/connect/alltrials-campaign-supports-greater-clinical-trial-transparency
23. Thomas K, Schmidt MS. Glaxo Agrees to Pay $3 Billion in Fraud Settlement. [Internet] The New York Times. 2012 July 2. Available from: http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html
24. Tucker K, Branson J, Dilleen M, et al. Protecting patient privacy when sharing patient-level data from clinical trials. BMC Med Res Methodol. 2016;16(1):77.
25. Price WN, Minssen T. Will clinical trial data disclosure reduce incentives to develop new uses of drugs? Nat Publ Gr. 2015;33(7):685-6.
26. Roin BN. Solving the problem of new uses [Internet]. Social Science Research Network. 2013 October 10. Available from: http:// dx.doi.org/10.2139/ssrn.2337821

Is Brand Name Best? Brand Name Versus Generic Pharmaceuticals in Clinical Practice

Andrea Bakker, BSc, Pharmacology and Therapeutics[1]

[1] Faculty of Medicine, Univeristy of Ottawa

ABSTRACT

In the last few years some of the biggest 'blockbuster drugs', that is the drugs that make pharmaceutical companies billions of dollars, have lost their patents. This means that generic manufacturers are able to produce these medications at a fraction of the cost. But what really differentiates generics from brand name medications? This commentary will explore how differences in licensing affect drug efficacy and how the pharmaceutical landscape in Canada affects patient care.

RÉSUMÉ

Au cours des dernières années, les brevets de certains des plus grands « médicaments vedettes », c'est-à-dire des médicaments qui rapportent des milliards de dollars aux compagnies pharmaceutiques, sont arrivés à échéance. Cela signifie que les fabricants de médicaments génériques peuvent désormais produire ceux-ci à moindre coût. Mais qu'est-ce qui différencie véritablement les médicaments génériques de ceux d'origine? Ce commentaire examinera comment les différences en ce qui a trait aux licences affectent l'efficacité des médicaments, et comment le panorama pharmaceutique au Canada affecte les soins de santé.

INTRODUCTION

It's a common scenario: standing in front of the cereal isle debating between 'Cheerios' and the less-than-appealing 'Toasted Oat' generic version. Sure, Cheerios is the original and has that ever persuasive bee on the box, but the generic is superior in terms of cost. Of course, the generic tastes about the same, but depending on the store, the generic version is slightly different–nothing compares to the consistency of a bowl of tried and true Cheerios. A similar decision is made by physicians when deciding between brand name medications and generics. Since 2010, several 'blockbuster drugs', which are drugs that make pharmaceutical companies billions of dollars, have lost their patents [1]. This phenomenon is commonly referred to as the 'patent cliff' [1]. As another 'patent cliff' is set to occur from 2014 to 2020 [1], we will see generic manufacturers take over the production of brand name medications at a fraction of the cost. For example, 2015 saw Abilify, a popular antipsychotic, and Lantus, a long-acting insulin, lose their patents [1]. What does this mean for patients? Are brand name drugs clinically superior? How are generic and brand name drugs licenced and what does this mean in terms of their efficacy and potency? This commentary will highlight the differences between brand name and generic drugs that prescribers may want to consider before putting pen to prescription pad.

The pharmaceutical landscape in Canada underwent a drastic change when, in 1969, legislation allowed Canada to import generic drugs [2]. This resulted in a large influx of generic pharmaceuticals into the Canadian market and was followed by additional reform that mandated generic substitution for brand name drugs unless explicitly specified by the physician [2]. Today, due to automatic substitution laws in Ontario, even if a physician prescribes Lipitor, the patient will receive generic Atorvastatin [3]. The physician can try to specify that the brand name drug is preferred by writing "Lipitor, no subs" [3], however the increased cost of the brand name may not be covered by insurance programs. For example, patients on the Ontario Drug Benefit program will be required to try two interchangeable generic products and have a documented Adverse Drug Reaction (ADR) to both before being eligible to receive the brand name medication at no additional charge [4]. In addition to receiving the generic version, automatic substitution states that the patient is to receive the least expensive generic brand of Atorvastatin with which the pharmacy is currently stocked [3]. In order to understand how automatic generic substitutions might affect patient care, we must first understand how the two types of drugs are produced and licensed.

Keywords: Pharmaceuticals; Generic; Brand Name

DRUG DEVELOPMENT

In terms of drug development (**Table 1**), brand name pharmaceutical companies are responsible for the research and development (R&D) of their new medications, including arranging preclinical and clinical trials [5]. This process usually takes over ten years and has an estimated cost of $2.6 billion per drug [6]. Many drugs do not pass these trials. For every 5,000 to 10,000 chemicals that enter preclinical testing, only one makes it onto the market [7]. If drug trials are successful, the pharmaceutical company is warranted a 20-year patent which begins early in drug

Table 1: Drug development differences between brand name and generic pharmaceuticals

Process	Brand Name	Generic
Research and Development	Performs [5]	Does not perform [5]
Trials	Preclinical [5] Clinical Trials (Phases I, II, III) [5]	Pharmaceutical equivalence [7] Bioequivalence [7]
Cost for Development	> 10 years $2.6 billion USD [6]	2-3 years $3-10 million USD [5]
Patent	20 years[8]	None

Table 2: Differences in the drug product between brand name and generic

	Brand Name	Generic
Components	Active Component	Same active molecule Different excipients and packaging [9]
Cost	50% higher than generic [9]	
Coverage		Covered by insurance, used in hospital
Packaging	Consistent	Changes depending on generic in stock
Target Audience	Physicians, Patients	Pharmacies

development, thus only affording the company about ten years of protected time on the market [8]. Conversely, generic pharmaceutical companies do not develop new drugs [5]. Instead, once brand name drug patents expire, the generic pharmaceutical company submits an application for drug manufacturing. The generic company is only required to prove pharmaceutical equivalence and bioequivalence to the brand name drug [7]. This process only takes two to three years and costs $3-10 million [5].

DIFFERENCES IN DRUG PRODUCT

In terms of differences in the product itself (**Table 2**), brand name drugs contain the original combination of the active ingredient and binders that was tested in clinical trials [9]. Brand name drugs often cost at least 50% more than generic [9] but have the advantage of maintaining consistent packaging and therefore are more recognizable to physicians and patients. Generics, however, have the same active molecule but are bound by different excipients and packaged differently [9]. They are more likely to be covered by insurance and are the default medications used in hospital. Unfortunately, the type of generic used, whether it be from Teva Pharmaceuticals or Apotex Pharmaceuticals for example, is subject to change depending what the pharmacy is using to stock their shelves [10]. Importantly, a patient may be taking warfarin from Teva Pharmaceuticals for several years, but if their pharmacy changes their supplier to Apotex, the patient may now be receiving Apotex warfarin which will look different and may have a different potency. This occurs unbeknownst to the prescribing physician. The potential implications of this occult change will be expanded upon in this commentary.

With all of these differences in mind, there are a few key distinguishing factors that physicians must consider before prescribing medications. These include differences in efficacy and packaging between generic and brand name pharmaceuticals.

DIFFERENCES IN DRUG EFFICACY

Differences in efficacy arise from the process in which generic drugs are approved. Generics must demonstrate pharmaceutical equivalence and bioequivalence to brand name drugs [7]. Pharmaceutical equivalents are pharmaceuticals that contain the same active ingredient in the same dosage, form, and route of administration as the brand name drug [11]. Bioequivalence is a pharmacokinetic equivalence and is demonstrated through a single-dose, two-treatment, crossover-designed study in normal adult volunteers [11]. In this study, the area under the curve (AUC), which represents drug absorption over time, and maximum drug concentration (Cmax) are measured [11]. These two values must have a 90% confidence interval (CI) that is between 80 - 125% of the brand name drug [11] (**Figure 1**). For example, if one were to look at the AUC for a generic drug, it could be only 90% of the brand name, however, as long as the CI falls between 80% and 125% of the brand name AUC, this drug would be approved. If it had a small CI, this would mean that patients taking the drug are usually receiving only 90% of what is expected. In addition, when pharmacies switch between different brands of generic medications, a process which often occurs unbeknownst to the physician, this could result in going from a generic delivering 90% of the expected drug to one delivering 110%. Theoretically, this could be a problem with drugs that have a narrow therapeutic index or a critical dose [11].

CLINICAL OUTCOMES WITH GENERIC VERSUS BRAND NAME MEDICATIONS

Several studies have attempted to address the theoretical difference in efficacy between generic and brand name medications.

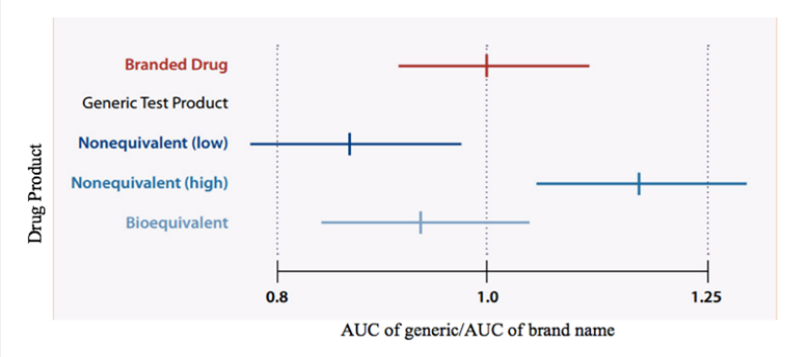


Figure 1: Possible results for testing generic drugs. The Area Under the Curve (AUC) of the generic drug is compared to the brand name. Two examples of drugs are shown that have 90% confidence intervals (CI) extending beyond the acceptable range. The bottom example falls within the viable range and would be accepted despite the fact that its AUC value is below the target value [13].

A recent case-control study of about 78,000 patients found no difference between generic and brand name antihypertensives in terms of hospitalization for cardiovascular disease [12]. This is in line with the fact that minor variations in blood pressure are unlikely to have a clinically noticeable impact on long-term outcomes. What about medications with a narrow therapeutic index? A recent review of 40,000 patients on warfarin demonstrated no statistically significant difference in international normalized ratio (INR) or dose adjustments after switching to generic drugs and no increase in adverse effects [14]. Nonetheless, on an individual level, the study found up to a 10% change in INR values after switching to generic [14]. Similarly, a recent meta-analysis of antiepileptic medications found no difference in the rates of uncontrolled seizures between generic and brand name phenytoin, carbamazepine, and valproic acid [15]. The researchers noted an increase in hospitalization when medication was changed from one generic brand to another (HR = 1.6 (1.1- 2.5)) but not for changing from brand name to generic [15]. This is in line with the concept that there could be more variability between different types of generic medications than between brand name and a given type of generic.

CONCERTA: A CASE-STUDY IN PHARMACOKINETICS

Recently, concerns arose with regards to the generic versions of Concerta. Concerta, also known as methylphenidate, is a Central Nervous System (CNS) stimulant used for treatment of attention deficit hyperactivity disorder (ADHD). Anecdotal reports stated that certain generic versions of the medication were not effective [16]. There are currently three generic versions of Concerta being used in North America. Only Concerta and the Actavis generic formulation use a time-release technology called osmotic controlled-release oral delivery system (OROS), which is a special system that ensures slow release of the medication over 10 to 12 hours [16]. The other two generic versions do not use the OROS system [16]. A recent study provided objective evidence that the non-OROS generics provided inferior treatment of ADHD symptoms compared to OROS formulations mostly due to inadequate duration of action [16]. In light of the approval process discussed above, this makes sense. Both formulations have the same dose of the same active molecule. They will both result in similar amounts of drug absorbed (AUC) and similar maximal concentrations (Cmax), meaning that non-OROS drugs would be approved under the current standards. Nonetheless, the time at which the maximal dose is reached differs between the non-OROS and OROS formulations which results in an inferior clinical outcome with non-OROS generics.

APPEARANCE OF MEDICATIONS IS IMPORTANT FOR PATIENT COMPLIANCE

Another important difference between generic and brand name drugs is appearance. Only weeks into my clinical rotations, I soon learned that patients rarely remember the names of their medications. They do, however, remember medication appearance. It is common knowledge in the medical field that 'the blue puffer' is salbutamol, but pragmatic patients only remember that they should take the blue puffer if they cannot breathe. Imagine the problems that would arise if salbutamol was changed to a red puffer.

A recent case control study in the Annals of Internal Medicine confirmed this. It analyzed patients post-myocardial infarction taking cardiac medications [17]. The study identified patients who discontinued medication and recorded if there was a recent change in pill shape or colour [17]. The study found that the odds of non-persistence increased 34% and 66% after a change in pill colour and pill shape, respectively [17]. The researchers attributed the discontinuation to patient skepticism and mistrust of the pharmacy when pill appearance was changed [17]. This is important because the packaging of brand name drugs is consistent, whereas the packaging of generics is not only different but can

change if the pharmacy changes their generic supplier. This can result in patient non-compliance.

CONCLUSION

In conclusion, as we approach another 'patent cliff', I suggest thinking of generic and brand name drugs in a similar way to how one shops at the grocery store. Generally, generics are less expensive and have comparable efficacy, but have the disadvantage of having packaging that is inconsistent between generic brands. They work well, but switching to a generic from a brand name and switching between generics is the hardest part. When selecting medications, it is important to consider the differences in medication licensing and the implications that it may have on your patient. A higher degree of vigilance is paramount for medications in which pharmacokinetics are crucial, because these generic medications may pass the approval process but still possess key differences that could affect patient outcomes. Finally, remember that despite what is written on the prescription, patients receive generic medications by default. The brand of generic depends on the pharmacy and can change regularly, resulting in patient confusion. So, is brand name best? Well like most things in medicine, the answer is: it depends.

REFERENCES

1. Kakkar AK. Patent cliff mitigation strategies: Giving new life to blockbusters. Expert Opin Ther Pat. 2015;25(12):1353-9.
2. Sanders JC. Limited lists of drugs: Lessons from abroad. Br Med J (Clin Res Ed). 1985;290(6469):710.
3. Anis AH. Pharmaceutical policies in Canada: another example of federal-provincial discord. CMAJ. 2000;162(4):523-6.
4. Regulation Amendments in support of Sustainability and Access for the Ontario Drug Benefit Program [Internet]. Ministry of Health and Long-Term Care; 2015 Sep 17 [cited 2016 Jan 30] Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/notices/fq_exec_office_20150917_1.pdf
5. Pharmaceutical Industry Profile [Internet]. Industry Canada; 2015 Jan 19 [cited 2015 Nov 2]. Available from: https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html.
6. Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion [Internet]. Tufts Centre for the Study of Drug Development; 2014 Nov 14 [cited 2015 Nov 2] Available from: http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.
7. Klees JE, Joines R. Occupational health issues in the pharmaceutical research and development process. Occup Med. 1997;12(1):5-27.
8. Heilman RD. Drug development history, "overview," and what are GCPs? Qual Assur. 1995;4(1):75-9.
9. Chawla K, Tofighi T, Agarwal A, Thomas J, Mondal T. A Global Comparison Between Brand-Name and Generic Drugs. Indian Journal of Pharmacy Practice. 2014;7(3):23-8.
10. Hollis A. The importance of being first: evidence from Canadian generic pharmaceuticals. Health Econ. 2002;11(8):723-34.
11. Kefalas CH, Ciociola AA. The FDA's generic-drug approval process: similarities to and differences from brand-name drugs. Am J Gastroenterol. 2011;106(6):1018-21.
12. Corrao G, Soranna D, Merlino L, Mancia G. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: Evidence from a large population-based study. Eur J Clin Invest. 2014;44(10) 933-9.
13. Fraser T, Tilyard M. BPJ, special edition: generics [Internet]. Dunedin, New Zealand: bpacnz Ltd; 2009 Jul. [cited 2016 Jan 1]. Available from: http://www.pharmac.govt.nz/2009/08/25/bpjse_generics_2009.pdf.
14. Dentali F, Donadini MP, Clark N, et al. Brand name versus generic warfarin: A systematic review of the literature. Pharmacotherapy. 2011;31(4):386-93.
15. Kesselheim AS, Stedman MR, Bubrick EJ, et al. Seizure outcomes following the use of generic versus brand-name an epileptic drugs: A systematic review and meta-analysis. Drugs. 2010;70(5):605-21.
16. Lally MD, Kral MC, Boan AD. Not All Generic Concerta Is Created Equal: Comparison of OROS Versus Non-OROS for the Treatment of ADHD. Clin Pediatr (Phila). 2016;55(13):1197-201.
17. Kesselheim AS, Bykov K, Avorn J, Tong A, Doherty M, Choudhry NK. Burden of changes in pill appearance for patients receiving generic cardiovascular medications after myocardial infarction: Cohort and nested case-control studies. Ann Intern Med. 2014;161(2) 96-103.

Multiple Comparisons in Variation of Care Research

Vinay Prasad, MD, MPH[1]; Andrew Oseran, MD, MBA[2]

[1] Oregon Health & Science University
[2] Massachusetts General Hospital

ABSTRACT

Research in hospital variation is important and currently very popular. However, due to the methods employed in such studies—namely, the retrospective mining of large datasets and the use of several alternative variation groupings—some results may be spurious. In this commentary, we perform an empirical analysis of the 50 most highly cited and the 50 most recent papers focusing on variation in medical care. Across these studies, we identify at least 13 unique groupings and could find no single instance where a medical practice was found not to vary. We go on to discuss one example of variation—statin use—in more detail to elucidate the tensions that these studies often create. Together, these results suggest that multiple hypothesis testing is a concern for variation research. Finally, we outline strategies to mitigate this concern.

RÉSUMÉ

La recherche sur la variation hospitalière est importante et actuellement très populaire. Toutefois, en raison des méthodes employées dans de telles études—notamment, l'extraction rétrospective de grands ensembles de données et l'utilisation de plusieurs groupements de variation alternatifs—certains résultats peuvent être fautifs. Dans ce commentaire, nous effectuons une analyse empirique des 50 articles les plus citées et des 50 articles les plus récents se concentrant sur la variation dans les soins médicaux. Dans ces études, nous identifions au moins 13 groupements uniques, et ne pouvions trouver aucun cas où une pratique médicale ne variait pas. Nous discutons ensuite d'un exemple de variation—dans l'utilisation de statines—en plus de détails afin d'élucider les tensions que ces études suscitent souvent. Collectivement, ces résultats suggèrent que la mise à l'essai de multiples hypothèses est une préoccupation lors de la recherche sur la variation. Finalement, nous décrivons des stratégies pour atténuer cette préoccupation.

INTRODUCTION

Variation in medical care that is not explained by patient preferences or characteristics and does not result in improved health outcomes is inappropriate. This metric often serves as the subject of public policy deliberation and intervention. The body of evidence now documenting such variation is immense. A PubMed search for "variation in care" yields over 23,000 entries (July 8, 2013), and the same terms generate over 2 million results on Google Scholar (July 8, 2013). The seminal illustration of variation research, the Dartmouth Health Atlas, describes variation across 306 hospital referral regions (HRRs) in the United States [1].

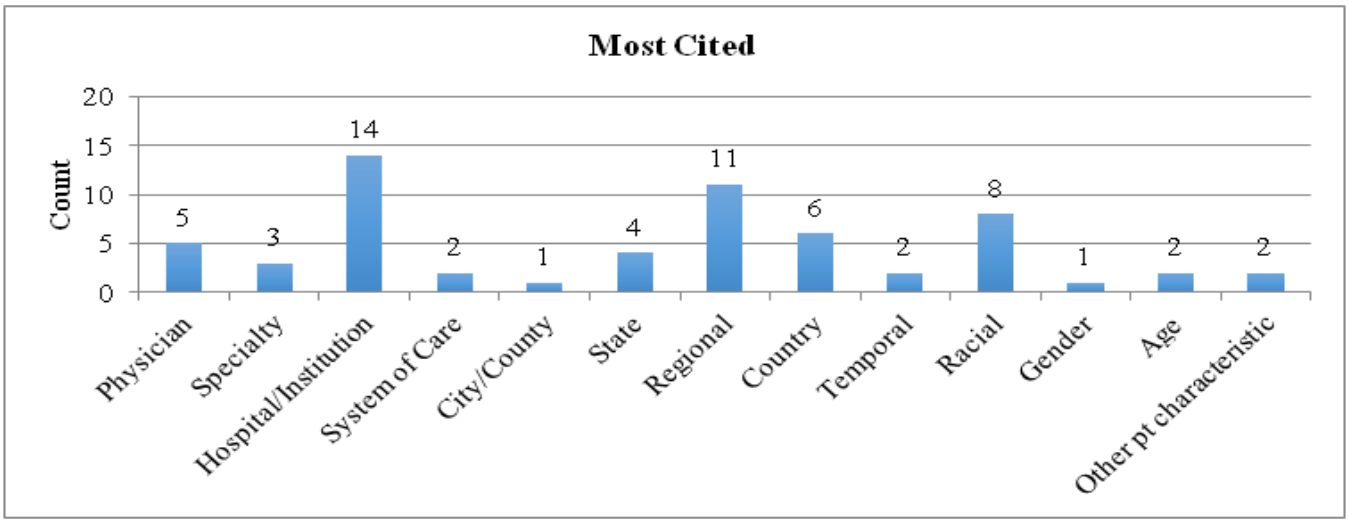
Others have analyzed variation across groupings other than HRRs. For instance, Zhang et al. examined variation across 3,436 hospital service areas (HSAs) in the United States. They found that the highest spending HSAs were only loosely correlated with high spending HRRs [1]. These results suggest that targeting variation by HRR is neither a sensitive nor specific strategy to identify the source of unwarranted practice [1]. Other research efforts have examined variation based on race, physician specialty, individual physicians, individual hospitals, patient age, other patient characteristics, countries, states, cities, neighbourhoods, and more. Importantly, these studies are often performed in large data sets, such as Medicare administrative databases, and are thus likely overpowered to identify small but significant differences between groups.

Keywords: Variation; Healthcare Quality; Clinical Outcomes; Comparative Effectiveness

Unexplained variation research is very popular and often provocative, likely thousands of researchers embark on projects studying variation. Because these studies are nearly always done retrospectively, and because such analyses can be conducted easily with modern computing, for all of the variation studies that have been published, many more analyses—possibly thousands—remain unpublished [2]. In short, research papers that find unexplained variation in medicine may represent only the tip of the iceberg, with many more studies hidden beneath the surface. When many observational analyses are conducted with diverse definitions, datasets, and hypotheses, the possibility exists that a large portion of the literature is spurious—reflecting what researchers and editors believe is plausible, rather than the truth about patterns of inappropriate care [2,3].

To illustrate this point, we set out to characterize the number of ways in which variation is analyzed in a representative sample of variation of care research. Specifically, using Thomson Reuters Web of Science, we identified the 50 most highly cited and the 50 most recent studies of variation in a medical practice in the biomedical literature. Our search was conducted on January 31, 2013, using "Variation" in the title field, and restricting results to

A



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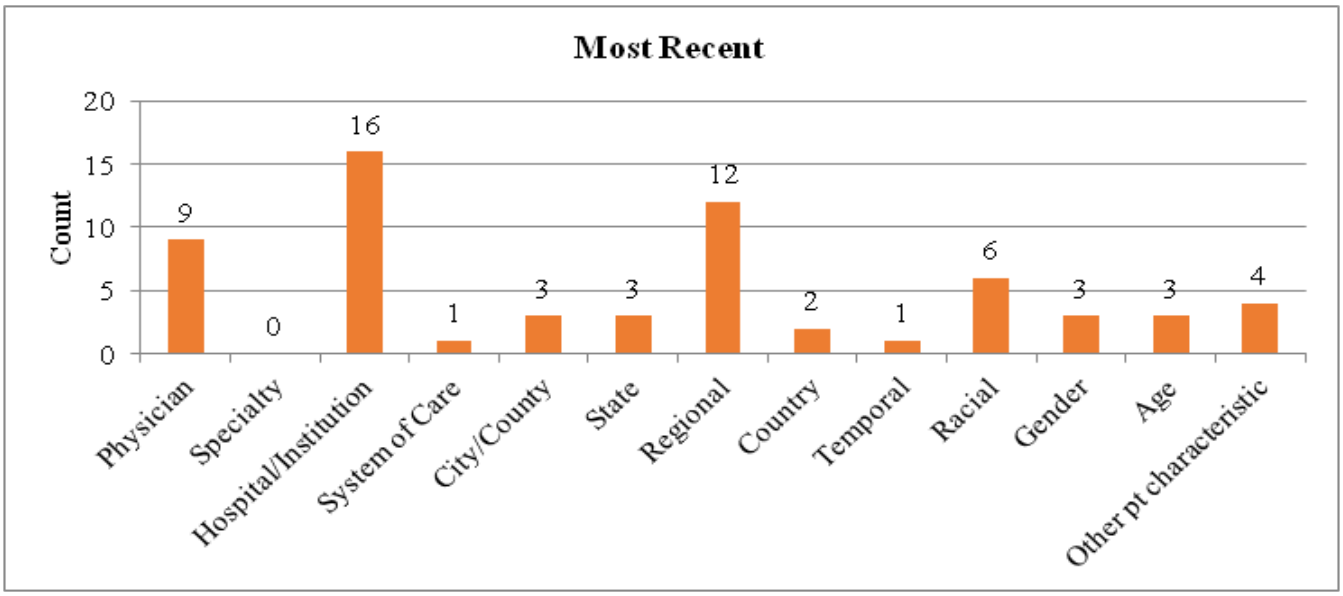

Figure 1: Count of categorical groupings employed in (A) the 50 most highly cited variation of care papers, and in (B) the 50 most recent variation of care papers

the category of "General Internal Medicine."

Our search generated 2,836 results. One reviewer (A.O.) then selected the 50 most highly cited and the 50 most recent papers that assessed variation in a medical practice. Each included article was read in full, and the metric(s) by which variation was studied was recorded in a Microsoft Excel spreadsheet. As such, each article could perform analyses and subsequently be coded in multiple categories.

The 50 most highly cited articles examined variation 61 times, and the 50 most recent articles examined variation 63 times. The most common comparisons were made between hospitals (14 times in the most cited grouping, and 16 times in the most recent grouping) and between regions (11 and 12, respectively). **Figure 1** shows common ways in which variation was analyzed among the 50 most highly cited and 50 most recent papers of variation in medical care. In short, in a relatively small sample of 100 variation papers, at least 13 alternative groupings were examined for variation.

Many of the challenges created by variation research are illustrated by a study of statins among dialysis patients. As of 2012, two large, multicenter randomized control trials (RCTs) showed no benefit of statin therapy among patients who were on hemodialysis, despite their high cardiovascular risk [4,5]. A third RCT, which combined a statin with ezetimibe, and included both dialysis and chronic kidney disease patients, found a reduction in myocardial infarction risk, no improvement in coronary death, and a trend towards increased death from all causes with the use of lipid therapy [6]. Thus, the totality of evidence suggests that statins have no role among hemodialysis patients.

A subsequent variation paper assessed variation in the use of statins among dialysis patients [7]. The results of this paper were as follows: use varied by patient sex, age, race, smoking status, functional status, whether diabetes was the cause of end stage renal disease, substance abuse status, number of comorbidities, and geography (state to state). The authors conclude that the variation they observed "may well reflect a lack of consensus regarding optimal management" [7]. Some of the variation they observed was not surprising; for instance, patients with more comorbidities were more likely to be on a statin. However, others were counterintuitive; for instance, men were less likely than women to use statins. With so many analyses conducted (and the possibility of other unreported analyses), it is difficult to know which of these findings are true. Is there a systematic bias among physicians to give statins to diabetic patients on dialysis? Probably, yes. Is there a bias to withhold statins from men on dialysis? We find this hypothesis implausible. The latter may simply be an artefact of multiple hypothesis testing.

The key question stemming from this line of reasoning becomes: Is knowledge of these variations useful? We already know that no trial has shown which (if any) patients on dialysis benefit from statins, and two trials have shown no benefit. Arguably, no patient on hemodialysis should be on a statin. Regarding variation research, Krumholtz argues that "the goal is not to eliminate variation but to guarantee that its presence throughout health care systems derives from the needs and preferences of patients" [8]. However, when a medication carries a real risk of side effects and no chance of benefit, there is no compelling need for a patient to take it and it is hard to imagine any preference that overrides these facts.

If the authors wish to show that statin use continues in this population despite RCT data suggesting that it is not beneficial, they only need to show its rate of use, not the countless groups among which it varies. If the authors instead doubt the validity of the RCT that yielded negative results on the use of statins in this population, they need to offer alternative data showing the benefit of statins. However, if the authors wish to show that statins continue to be prescribed to some dialysis patients but not to others, then variation is the right test. With that said, this test should be based on a priori hypotheses, and corrected for multiplicity.

We have outlined some of the problems with variation studies. They are conducted in cases where there is clear evidence, as well as at times when there is no consensus. Datasets used are large and ubiquitous, and variation can be queried across many alternative groupings. As such, many of the results of variation papers may not reflect systemic biases in the use of a treatment, but may rather be an artefact of multiple hypothesis testing.

To improve upon validation studies, we propose that they be conducted only in cases where the evidence base for a practice is genuinely uncertain. When conducted, all proposed groupings should be pre-specified and noted in the paper. Ideally, the protocol for the study should be registered, as others have proposed [2]. The number of dimensions across which variation is queried should be limited to minimize spurious results. Finally, falsification testing should be added to variation papers. Specifically, if variation is used to make claims that reimbursement schemes drive discordant use, then interventions that are not subject to those maligned incentives should be shown not to vary. In fact, in our examination of this subject, we could find no investigation of variation that satisfied Krumholz's mark: where all variation is due solely to legitimate patient characteristics and preferences [8]. If indeed no such practice can be shown to meet this standard, then the standard itself should be reconsidered.

REFERENCES

1. Zhang Y, Baik SH, Fendrick AM, Baicker K. Comparing local and regional variation in health care spending. N Engl J Med. 2012;367(18):1724-31.
2. Ioannidis JA. The importance of potential studies that have not existed and registration of observational data sets. JAMA. 2012;308(6):575-6.
3. Prasad V, Gall V, Cifu A. The frequency of medical reversal. Arch Intern Med. 2011;171(18):1675-6.
4. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395-407.
5. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238-48.
6. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92.
7. Wetmore JB, Mahnken JD, Mukhopadhyay P, et al. Geographic variation in HMG-CoA reductase inhibitor use in dialysis patients. J Gen Intern Med. 2012;27(11):1475-83.
8. Krumholz HM. Variations in health care, patient preferences, and high-quality decision making. JAMA. 2013;310(2):151-2.

Inclusive Health Conference: Conference-Based Education as an Intervention to Address Medical Education Deficits

Jocelyn Andruko, BHSc[1]; Brandon Christensen[1]; Melanie Lewis, MD, FRCPC[2]

[1] University of Alberta Faculty of Medicine and Dentistry
[2] University of Alberta Faculty of Medicine and Dentistry, Professor of Pediatrics

ABSTRACT

Introduction: Physicians are responsible for the health of all patients, but medical students receive inadequate training on the healthcare needs of LGBTQ (Lesbian, Gay, Bisexual, Transgender, and Queer) patients [1]. Education about cultural issues and proper terminology are also under-addressed. Healthcare practices that cannot demonstrate inclusivity risk alienating patients and perpetuating barriers to patient care for sexual and gender minorities [2].

Methods: In 2013, medical students created the Inclusive Health Conference to address these educational deficits. Experts were invited to present a curriculum including disorders of sexual development, HIV pre-exposure prophylaxis, care for transgender patients, and development of inclusive practices. Self-identified sexual minority patients were also invited to share their experiences. Following these sessions, healthcare professionals and students were asked to complete a survey on knowledge and level of comfort with LGBTQ care.

Results: A majority of respondents stated that they "better understand LGBTQ health issues" (2015 mean 4.39, n = 41; 2016 mean 4.31, n = 52), "better understand social issues related to LGBTQ healthcare" (2015 mean 4.32, n = 41; 2016 mean 4.31, n = 52) and "feel more comfortable exploring and discussing these issues with LGBTQ people" (2015 mean 4.43, n = 41; 2016 mean 4.17, n = 52).

Conclusions: Based on survey results, this was a successful solution to a critical omission in medical curricula. Of note, the conference also drew attention to this important issue, led to financial sponsorship by the University of Alberta's Faculty of Medicine and Dentistry, initiated curriculum updates, and inspired similar events at other institutions.

RÉSUMÉ

Introduction: Les médecins sont responsables de la santé de tous les patients, mais les étudiants en médecine reçoivent une formation inadéquate en ce qui a trait aux besoins de soins de santé des patients LGBTQ (lesbienne, gai, bisexuel, trans et queer) [1]. Les enjeux culturels et la terminologie appropriée sont également trop peu abordés au cours de la formation. Les pratiques de soins de santé qui ne font pas preuve d'inclusion risquent d'aliéner les patients et de perpétuer les obstacles aux soins de santé pour les personnes de minorités sexuelles et de genre [2].

Méthodes: En 2013, des étudiants en médecine ont créé la conférence Inclusive Health (santé inclusive) afin de combler ce manque éducationnel. Des experts ont été invités à présenter un curriculum qui incluait des désordres de développement sexuel, la prophylaxie préexposition contre le VIH, les soins aux patients transgenres, et l'élaboration de pratiques inclusives. Des patients ayant volontairement déclaré leur appartenance à une minorité sexuelle ont également été invités à partager leurs expériences. À la suite de ces séances, les professionnels de la santé et les étudiants ont rempli un sondage sur leurs connaissances et leur niveau de confort dans la prestation des soins de santé aux personnes LGBTQ.

Résultats: La majorité des personnes interrogées ont affirmé « mieux comprendre les problèmes de santé des personnes LGBTQ » (moyenne de 4,39 en 2015, n = 41 ; moyenne de 4,31 en 2016, n = 52), « mieux comprendre les enjeux sociaux liés à la prestation des soins de santé aux personnes LGBTQ » (moyenne de 4,32 en 2015, n = 41 ; moyenne de 4,31 en 2016, n = 52) et « se sentir plus à l'aise d'explorer et de discuter de ces problèmes avec les personnes LGBTQ » (moyenne de 4,43 en 2015, n = 41 ; moyenne de 4,17 en 2016, n = 52).

Conclusions: En se fondant sur les résultats du sondage, la conférence s'est avérée efficace pour contrer une omission importante dans les curriculums médicaux. En outre, la conférence a attiré l'attention sur cet important problème, a mené à un parrainage par la Faculté de médecine et de médecine dentaire de l'Université d'Alberta, a entraîné des mises à jour aux curriculums médicaux, et a inspiré des évènements semblables à d'autres établissements.

Keywords: LGBTQ; Lesbian; Gay; Bisexual; Transgender; Queer; HIV; Medicine; Global Health; Pediatrics; Inclusive Health; Community Engagement

INTRODUCTION

Healthcare Deficits

LGBTQ (Lesbian, Gay, Bisexual, Transgender, and Queer) individuals have additional and unique healthcare needs including higher rates of mental health issues, substance use, and sexually transmitted infections. LGBTQ youth also have higher rates of teen pregnancy [3].

Literature also demonstrates that LGBTQ populations are not receiving the healthcare they need to address those health concerns. Canadian LGBTQ people have been shown to be less likely to have a regular healthcare provider, and lesbian women in particular are less likely to have seen a family doctor or have cervical cancer screening within the past 12 months [4]. Even compared against other sexual and gender minorities, transgender patients have particular difficulty accessing good quality healthcare. In a recent study, amongst transgender persons, 21% admitted to avoiding emergency room (ER) care and 52% reported facing trans-negative ER experiences [5]. It has also been identified that 25% of transgender Ontarians obtain hormones from non-medical sources, 6.4% take non-prescribed hormones, and 2.3% have performed or attempted surgical procedures on themselves in an attempt to self-treat [6]. This is undoubtedly a population underserved by our current medical system.

Barriers to Healthcare

A number of studies have attempted to identify the etiology of this longstanding problem, which is likely complex and multifactorial. Particular moments of distrust or discomfort that LGBTQ patients experience with medical care include coming out to providers, fear of being denied safe care, providers' insistence about unnecessary pregnancy tests or contraception, and misidentification or mixing-up of preferred pronouns [2]. Physician self-reported discomfort was also significant, and mainly related to feeling underprepared or unable to provide adequate care [2].

Existing Educational Context

This physician discomfort is unsurprising in the context of existing medical education surrounding these issues. North American medical schools average 2 hours of dedicated LGBTQ content across all four years of medical school; 44 schools report zero dedicated hours during clinical years and 9 schools report zero dedicated hours over all four years. When surveyed, a majority of deans of medical education were dissatisfied with their institutions' coverage of LGBTQ-related topics [1]. If provided with proper education, it is reasonable to expect that physicians may be more comfortable caring for LGBTQ individuals, which may in turn reduce patient discomfort with accessing care and improve healthcare outcomes overall.

Educational Intervention

In response to a lack of a focused LGBTQ curriculum at their institution, the Sexual Orientation and Gender Identity Advocacy (SGA) committee, composed of medical students at the University of Alberta, developed an educational platform to share best practices in LGBTQ health. This initiative, starting in 2014, was an annual, one-day student-led conference to educate medical students, residents, physicians, and other healthcare professionals in social and medical issues related to sexual and gender minorities.

Study Objectives

As part of the ongoing evaluation of this conference, a survey was conducted among healthcare professional and student attendees in 2015 and 2016. The objective was to assess the efficacy of this student-led conference as a short-term educational intervention to improve knowledge and comfort with a specific set of topics. The primary outcome for this survey was self-assessed improvement in knowledge and comfort. It was hypothesized that attendees would report at least moderate improvement in knowledge and comfort with these topics after receiving formal teaching on this curriculum. Secondary outcomes included subjective written comments.

METHODS

Curriculum Development and Content

As existing curricula on these topics were not readily available at the time, curriculum objectives were developed using a community engagement model; individuals and experts in the community were consulted each year, approximately 8 months in advance, to collect a list of possible relevant topics and themes. Once an appropriate list of topics was agreed upon, the organizers worked within the community to develop a network of experts to present. Where possible, local individuals were chosen to provide an accurate context of the local LGBTQ community. Experts included MDs, PhDs, and specialists in education policy research.

In the development of this curriculum, there was a particular focus on including a balance of relevant topics, including HIV treatment and pre-exposure prophylaxis, disorders of sexual development, psychiatric and endocrinologic assessment of transgender individuals, and family planning for same-sex couples. Speakers and panels of LGBTQ community members sharing personal experiences were also included, to provide a perspective of lived experiences and challenges for this population.

A unique overall theme was also selected each year through the same community engagement model, to reflect current events and issues. In 2015, the focus was care for transgender patients, including a curriculum on hormone therapy for transgender teens. In 2016, the overall theme was care for at-risk populations of gay men, including new research about HIV pre-exposure prophylaxis and speakers with personal stories reflecting the intersectionality of LGBTQ individuals with other at-risk populations, including First Nations, homeless, addicted, and HIV-positive individuals. These yearly themes allowed the curricula to provide a greater focus on relevant and current information, while still allowing for a breadth of overall content.

Each conference included approximately 8 hours of curricular time, including didactic lectures (60%), interactive panels and discussions (20%), and small-group breakout sessions (20%) to maximize audience engagement. The 2016 conference was accredited to provide Continuing Medical Education (CME) accreditation for family physicians in attendance, to further motivate interested physicians to attend.

Survey Development

An optional survey (**Text Box 1**) was developed with the help of Dr. Kris Wells, an Assistant Professor at the University of Alberta's Faculty of Education, and a well-known expert in this field. The survey collected demographic information including gender, sexual orientation, and profession, as well as a score (out of 5) for agreement to each of the statements provided. Each question included the option "prefer not to answer" and identifying information was not collected. A space for subjective comments was included.

In the context of this survey, the previously stated hypothesis (that a moderate improvement in knowledge and comfort would be reported) was interpreted as a mean score of 4 for each question.

Inclusion and Exclusion Criteria

Inclusion criteria were that participants have self-identified as a physician, medical student, resident, or other healthcare professional. Exclusion criteria included those who were not able to attend at least one half-day of the Inclusive Health Conference in any of its most recent two yearly events. All conference attendees were evaluated for these criteria by student volunteers at registration. If criteria were met, the attendee was offered a paper survey by the study team, with verbal and written instructions and study information. Consent to participate was defined as returning a completed survey to the submission drop box provided.

Because no identifying information was collected, no data were excluded once surveys had been collected. There were no invalid entries that had to be excluded. Because all questions were made optional to protect confidentiality, some respondents did not complete every question, which is reflected by a slightly different total n in some results.

Both survey and study methods were reviewed and approved by the Research Ethics and Management board at the University of Alberta.

RESULTS

Study Population

An analysis of demographic information revealed that this group of attendees were different from the general population in several ways, including a greater proportion of women and of sexual minorities (**Table 1**). Despite targeting curriculum development and advertising towards physicians, residents, and students, the greatest proportion of attendees were nurses, medical students, and nursing students (**Table 2**).

Text Box 1: Example Survey

Please rate your agreement with the following statements:

1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree

After attending this conference,

I better understand LGBTQ health issues. 1 / 2 / 3 / 4 / 5
I better understand social issues related to LGBTQ healthcare. 1 / 2 / 3 / 4 / 5
I feel more comfortable exploring and discussing these issues with LGBTQ people. 1 / 2 / 3 / 4 / 5
I feel more comfortable working with LGBTQ patients. 1 / 2 / 3 / 4 / 5
I feel compelled to learn more about these topics. 1 / 2 / 3 / 4 / 5
I know where I can find more information about these topics. 1 / 2 / 3 / 4 / 5

Primary Outcome

Overall mean scores for each statement were found to be positive, all above 4.00 (**Table 3**). Highest scores were reported for the statement, "I feel compelled to learn more about these topics," which reflects an understanding of the importance of these educational topics.

Secondary Outcome

A subgroup analysis was performed for mean scores between demographic groups (**Tables 4** and **5**). Surprisingly, mean scores were notably higher for female attendees compared to male attendees. However, there was no significant difference in reported scores between individuals of different sexual orientations.

Subjective Comments

Two reviewers independently read these comments, and agreed upon overall themes. Positive comments reflected particular appreciation for panel discussions and personal stories, as well as for sessions on treatment for transgender patients (assessing readiness for transition, teaching on hormonal therapy, and indications for referral to specialists). Negative comments mainly suggested to focus less on the yearly theme (men who have sex with men, or transgender health) and to provide printed presentation slides.

DISCUSSION

Study Merits and Limitations

The degree to which these positive results can be interpreted is limited by a number of factors, the most obvious being the nature of self-assessment as an effective evaluation tool. Self-assessed measures of confidence or competence are poor surrogates for measuring actual achievement, and might show a large improvement where minimal change has taken place.

The validity of these results may also be limited by selection bias: as it was impossible to randomize participants and to protect confidentiality, this study did not record participants who accepted surveys but did not submit responses. As a result, the demographics measured on this survey may differ from the overall population of healthcare professionals. Those who attended potentially have personal interest in issues presented, and therefore may be motivated to overstate a positive response. On the other hand, this population may also be more likely to be involved with the LGBTQ community to start with, so may already understand objectives presented and learn nothing new. Given these opposing factors, it is difficult to know whether the data might be skewed more positive or negative. With future evaluation studies, our research team hopes to minimize these biases.

Despite these limitations, given such positive survey feedback, it may still be reasonable to suggest that this educational initiative has been effective, especially given the context of limited or entirely absent formal curricula on these topics.

In this context, it is also important to consider secondary outcomes, which included both subjective comments and a subgroup analysis. It is difficult to explain the meaning of the difference between self-reported scores for male and female respondents; the study team hopes to elicit whether and how this finding is significant on future studies. It is interesting to note that there was no significant difference between responses from heterosexual, homosexual, and bisexual groups; this may suggest that the information presented is not widely understood among LGBTQ communities, even those with enough interest in healthcare to attend such a conference, and further highlights the need for expertise among healthcare professionals. Despite targeting both curriculum development and advertising efforts at medical

Table 1: Demographics by gender and sexual orientation.

	2015	2016	Total
Gender			
Male	12 (29.3%)	15 (30.0%)	27 (29.7%)
Female	29 (70.7%)	35 (70.0%)	64 (70.3%)
Sexual Orientation			
Heterosexual	22 (55.0%)	27 (55.1%)	49 (55.1%)
Homosexual	9 (22.5%)	13 (26.5%)	22 (24.7%)
Bisexual	3 (7.5%)	7 (14.3%)	10 (11.2%)
Other	6 (15.0%)	2 (4.1%)	8 (9.0%)

Table 2: Demographics by health profession.

Health Profession	2015	2016	Total
Nurse	14	22	36
Nurse Practitioner	0	1	1
Physician	2	2	4
Psychologist	1	2	3
Pharmacist	0	1	1
Pharmacy Technician	0	1	1
Occupational/Physical Therapist	2	1	3
Social Worker	1	0	1
Health Education	3	2	5
Nursing Student	6	5	11
Medicine Student	10	10	20
Pharmacy Student	2	1	3
Medical Lab Science Student	0	1	1
Psychology Student	0	1	1
Occupational/Physical Therapy Student	0	1	1
Total	41	51	92

Table 3: Mean scores by survey statement.

Statement	2015		2016	
	Mean	Standard Deviation	Mean	Standard Deviation
I better understand LGBTQ health issues	4.39	0.703	4.31	0.612
I better understand social issues related to LGBTQ healthcare	4.32	0.650	4.31	0.673
I feel more comfortable exploring and discussing these issues with LGBTQ people	4.43	0.712	4.17	0.793
I feel more comfortable working with LGBTQ patients	4.44	0.594	4.17	0.760
I feel compelled to learn more about these topics	4.66	0.530	4.54	0.727
I know where I can find more information about these topics	4.28	0.909	4.25	0.789

Table 4: Subgroup analysis by sexual orientation.

Statement	2015			2016		
	Mean (Hetero-sexual) n = 22	Mean (Homo-sexual) n = 9	Mean (Bi-sexual) n = 3	Mean (Hetero-sexual) n = 27	Mean (Homo-sexual) n = 13	Mean (Bi-sexual) n = 7
I better understand LGBTQ health issues	4.41	4.30	4.67	4.33	4.14	4.57
I better understand social issues related to LGBTQ healthcare	4.41	4.30	4.33	4.37	4.15	4.57
I feel more comfortable exploring and discussing these issues with LGBTQ people	4.32	4.60	4.67	4.22	4.08	4.00
I feel more comfortable working with LGBTQ patients	4.45	4.60	4.33	4.26	4.00	4.29
I feel compelled to learn more about these topics	4.64	4.80	5.00	4.52	4.54	4.86
I know where I can find more information	4.36	4.20	4.00	4.15	4.00	4.86

Table 5: Subgroup analysis by gender.

Statement	2015		2016	
	Mean (Male) n=12	Mean (Female) n=29	Mean (Male) n=15	Mean (Female) n=35
I better understand LGBTQ health issues	4.08	4.52	3.93	4.46
I better understand social issues related to LGBTQ healthcare	4.17	4.38	4.00	4.46
I feel more comfortable exploring and discussing these issues with LGBTQ people	4.33	4.46	3.80	4.31
I feel more comfortable working with LGBTQ patients	4.25	4.52	3.73	4.40
I feel compelled to learn more about these topics	4.42	4.76	4.47	4.63
I know where I can find more information about these topics	3.79	4.48	3.62	4.49

students, residents, and physicians, and having a planning committee almost entirely of medical students, there was a wide variety of healthcare professions represented among attendees at this conference. This may reflect not only the greater number of non-physician healthcare professionals in our area, but the relevance of these topics for any healthcare professional.

Subjective comments suggested that topics related to care for transgender patients and personal stories about patient experiences were the most helpful and well received by attendees. They also suggested that printed educational materials and a more general focus with less focus on the yearly theme may further improve this program. Organization of the Inclusive Health Conference in 2017 and future years will continue to improve based on this feedback.

Other Results

There were a number of other results not directly studied, but with strong implications in understanding the value of this conference as an educational initiative. The most notable of these was the faculty attention directly generated by this conference's success. Following the first event in 2014, organizers and leaders were invited to a curriculum development committee, to write learning objectives to solve the educational deficit they had attempted to address. Although there remains much work to be done, this strongly suggests that independent educational initiatives may impact long-term formal curriculum changes. After the success of the initial conference in 2014, the Faculty of Medicine and Dentistry also provided a $100,000 grant for continuing yearly events, which further demonstrates their attention and support. Student colleagues at the University of Calgary have also since developed an analogous event at their own school, which highlights the possibility of nation-wide spread for important curriculum updates.

The media and community attention generated by this conference is also notable: over the last two years of this conference, organizers were invited onto three different local news networks, have been interviewed for a number of local and online newspapers, and have received several prestigious awards from the University of Alberta and its associated residency programs. This demonstrates the ability of such events to generate awareness and concern in the greater academic and local community, which can further address social and educational issues in ways that are much more difficult to measure.

CONCLUSION

An anonymous survey was used to evaluate this educational initiative. These results were very positive; despite unavoidable biases, this reflects both a lack of formal education on these topics and the ability of a short-term educational conference to address that deficit. We hope this work may serve as inspiration for similar initiatives in other schools, as well as for more formal medical curriculum development. More work must be done in the development of this initiative, including targeting curricula at a wider group of healthcare professionals and curriculum evaluation using more objective measures of knowledge and improvement. Ultimately, we hope to provide a more comprehensive curriculum which can be used to develop more formal changes at medical schools across the country.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose. The University of Alberta's Faculty of Medicine and Dentistry provided funding for the conference initiative described, but did not financially support the associated research study.

REFERENCES

1. Obedin-Maliver J, Goldsmith ES, Stewart L, et al. Lesbian, gay, bisexual, and transgender-related content in undergraduate medical education. JAMA. 2011;306(9):971-7.
2. Harbin A, Beagan B, Goldberg L. Discomfort, judgment, and health care for queers. J Bioeth Inq. 2012;9(2):149-60.
3. Saewyc EM, Poon CS, Homma Y, Skay CL. Stigma management? The links between enacted stigma and teen pregnancy trends among gay, lesbian, and bisexual students in British Columbia. Can J Hum Sex. 2008;17(3):123-39.
4. Tjepkema M. Health care use among gay, lesbian and bisexual Canadians. Component of Statistics Canada, Catalogue no. 82-003-X Health Reports. 2008;19(1):53–64.
5. Bauer GR, Scheim AI, Deutsch MB, Massarella C. Reported emergency department avoidance, use, and experiences of transgender persons in Ontario, Canada: results from a respondent-driven sampling survey. Ann Emerg Med. 2014;63(6):713-20.e1.
6. Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A. Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. Am J Public Health. 2013;103(10):1830-6.

Ensuring a Safe and Qualitative Diagnostic Biopsy for Retroperitoneal Sarcomas

Kristin Kennedy Ambacher, BSc[1]; Andrea Marie Ibrahim, MSc[2]; Carolyn Nessim, MD, MSc, FRCSC, FACS[2,3]

[1] Faculty of Medicine, University of Ottawa
[2] Ottawa Hospital Research Institute, The Ottawa Hospital
[3] Division of General Surgery, The Ottawa Hospital

ABSTRACT

Retroperitoneal sarcomas represent one third of neoplasms in the retroperitoneum and as such are an important entity when evaluating masses in this area. They are often identified incidentally as they present with non-specific symptoms and are only detectable on physical exam when they have grown to a large size. This group of tumours is a challenge for physicians as it encompasses over 50 different histological subtypes and the course of treatment greatly depends on histopathological diagnosis. Biopsy of these lesions has recently become standard of care when evaluating a suspected retroperitoneal sarcoma. However, historically, there has been speculation over whether this practice promotes needle tract seeding resulting in local recurrence which has resulted in limited research on the topic. As such, there is a lack of literature describing the best parameters for a safe and effective biopsy of these lesions. Our ongoing research aims to identify biopsy parameters which yield a safe and qualitative diagnostic biopsy while minimizing complications and local recurrence with the goal of consistent and quality care for all patients presenting with retroperitoneal lesions.

RÉSUMÉ

Les sarcomes rétropéritonéaux constituent un tiers des néoplasmes du rétropéritoine, et représentent ainsi une entité importante lors de l'évaluation de masses dans cet espace. Ils sont souvent découverts fortuitement puisqu'ils se manifestent par des symptômes non spécifiques et sont seulement décelables à l'examen physique lorsqu'ils atteignent une taille considérable. Ce groupe de tumeurs représente un défi pour les médecins, car il comprend plus de 50 différents sous-types histologiques et le traitement dépend largement du diagnostic histopathologique. La biopsie de ces lésions est récemment devenue la norme en matière de soins pour l'évaluation d'un sarcome rétropéritonéal soupçonné. Toutefois, par le passé, certains ont suggéré que cette pratique puisse possiblement disséminer le cancer et causer une récidive locale, ce qui a limité la recherche sur le sujet. Ainsi, il existe un manque de littérature décrivant les paramètres optimaux pour effectuer une biopsie sécuritaire et efficace de ces lésions. Notre recherche en cours vise à identifier les paramètres de biopsie qui produisent une biopsie diagnostique sécuritaire et qualitative, tout en minimisant les complications et les risques de récidive locale, dans le but de fournir des soins uniformes et de haute qualité à tous les patients avec des lésions rétropéritonéales.

INTRODUCTION

Soft-tissue sarcomas are a relatively rare group of malignancies of mesenchymal origin arising from soft-tissues such as fat, muscle, nerves and blood vessels. This is in contrast to a more common subtype of sarcoma arising from bone. Soft-tissue sarcomas arise most commonly in the extremities (i.e. upper and lower limbs) and retroperitoneum, the space between the peritoneum and posterior abdominal wall containing the kidneys, pancreas and other associated organs [1,2]. While soft-tissue sarcomas only make up 1% of all adult cancers, retroperitoneal sarcomas represent 15% of soft-tissue sarcomas and one third of retroperitoneal tumours in general, stressing their low incidence and the role of speciality care for masses in this region [2–4].

Keywords: Retroperitoneal; Sarcoma; Qualitative biopsy; Biopsy Parameters

Retroperitoneal sarcomas are often asymptomatic and identified incidentally during imaging performed for other purposes. This is mostly attributed to the large area encompassed by the retroperitoneal space which allows significant growth before a mass is noticeable or symptomatic. In fact, tumours in this space under 5 cm in size are rarely detected [5–7]. Furthermore, the most common presenting symptoms for patients with a retroperitoneal mass are non-specific (pain, weight loss, early satiety, nausea and a palpable abdominal mass) and often occur later in the course of the disease [5,7]. Luckily, despite its late detection, sarcomas are often identified without distant metastases because of their propensity for local extension, often pushing structures aside but rarely violating fascial planes [8]. In addition, soft-tissue sarcoma are known to have a disinclination for lymphatic spread which limits their metastatic potential [9,10]. It is due to this that the

mainstay of treatment for retroperitoneal sarcoma is surgery with neo-adjuvant chemotherapy or radiation in certain cases [11,12].

Retroperitoneal sarcomas present a challenge in terms of diagnosis and treatment plan due to the large diversity of histological subtypes that all present in similar fashion [2]. In fact, the World Health Organization recognizes over 50 subtypes of soft-tissue sarcoma. A further challenge with respect to these lesions is the large number of tumours that mimic sarcoma on presentation and imaging but which require very different treatment strategies. The most common example of this is lymphoma, which is often difficult to distinguish from sarcoma on CT scans and is treated by chemotherapy alone, whereas sarcoma is treated surgically [13].

Owing to the vast differential diagnosis of a retroperitoneal mass, it has become apparent that obtaining a histopathological diagnosis is a critical step in the work-up and management of these tumours. This paper describes the current practices in the evaluation of suspected retroperitoneal sarcoma, the role of needle biopsy and the historical controversy surrounding its use. We will also describe our current ongoing research at The Ottawa Hospital led by Dr. Carolyn Nessim, surgical oncologist, to standardize biopsy methods to ensure prompt diagnosis and proper treatment planning for patients with suspected retroperitoneal sarcoma.

CURRENT MANAGEMENT PRACTICES

Initial investigations of retroperitoneal tumours, as with most undiagnosed neoplasms, begin with radiologic imaging, usually CT scans or MRI. Imaging is useful for evaluating the size and extent of the mass as well as screening for lymphadenopathy or distant metastases. Moreover, imaging is required for surgical and/or radiation therapy planning [11,14].

Following imaging, the common practice, and now standard of care, is to proceed with percutaneous biopsy of the mass [11,15]. This diagnostic approach is particularly important in suspected retroperitoneal sarcoma as although imaging can sometimes distinguish between a benign or malignant neoplasm, a histological diagnosis is important in dictating treatment plan [13]. Furthermore, treatment regimen and sequence can differ depending on the grade of the neoplasm. Core needle biopsy can differentiate between benign and malignant neoplasm with very high accuracy and correctly identifies the sarcoma histological subtype 88-90% of the time [3]. This allows the treating surgeon to distinguish between benign neoplasms that require observation and malignant sarcomas which require excision, as well as whether neo-adjuvant treatment is necessary for improving outcome.

For example, one of the most common types of retroperitoneal sarcoma is liposarcoma, a malignant soft-tissue sarcoma arising from adipose tissue that can present with well-differentiated or dedifferentiated cells. These two histological features are characterized by very different biologic behaviours and consequently require a different management plan [16]. Studies have only shown a reduction in local recurrence with neo-adjuvant radiation or chemotherapy for patients with dedifferentiated liposarcoma and not for patients with the well-differentiated subtype [16,17].

Therefore, due to its key role in determining management strategy, core needle biopsy in the evaluation of retroperitoneal masses is now internationally practiced. Moreover, core needle biopsy is recommended by the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG), a working group established by multi-sarcoma-excellence institutions across the world in 2013 in order to develop consensus documents on the approach to treat this difficult disease [18]. The consensus guidelines strongly suggest image-guided percutaneous core needle biopsy to accurately sample the lesion. In addition, they recommend ensuring sampling of the more solid, dedifferentiated tumour components, as determined by well-perfused areas in contrast-enhanced CT scans or MRI.

NEEDLE TRACT SEEDING

Biopsy of retroperitoneal masses has been used with caution due to the belief that the procedure could lead to seeding of cancer cells along the needle tract, and thereby facilitate local recurrence. This has been shown in case reports pertaining to other types of cancers; however, relatively little data has been available with regards to risk of recurrence along the needle tract for retroperitoneal sarcoma [15]. Within the last five years, retrospective studies have demonstrated minimal risk of seeding, indicating this is not a reason to avoid biopsy [19–21]. In fact, a recent retrospective review from three tertiary sarcoma-treating centres (including our group at the Ottawa Hospital) looking at biopsy complications in 540 patients with a median follow-up of 50 months found only 2 patients (0.37%) with a sarcoma recurrence in the presumed biopsy tract [22]. A separate study from Wilkinson et al. failed to identify a single patient in their 150-patient cohort who developed a biopsy-site recurrence. Furthermore, they did not identify any differences in local recurrence rates or overall survival when comparing patients who underwent biopsy to those who did not [21].

Biopsy of retroperitoneal sarcomas is also considered a safe procedure with minimal complications [18,23]. In the same 540 patient cohort mentioned previously, a second analysis described early complications of percutaneous biopsies of retroperitoneal masses in a subset of patients (n=288). Specifically, 7 (2.4%) bi-

opsies resulted in minor bleeding with no transfusions required, 3 (1%) patients reported significant pain which was managed effectively with acetaminophen and/or NSAIDs, and one patient (0.3%) required an unplanned admission to the hospital for 24 hours [22].

Despite the fact that biopsy is now gaining support for being a safe method of pre-operative diagnosis of retroperitoneal masses, there is still a lack of literature surrounding this topic. Specifically, there is a knowledge gap regarding the quality measures which ensure not only a safe biopsy but one with high diagnostic yield (the likelihood the test will provide a diagnosis). To date, only one paper has made recommendations for biopsy of soft-tissue and bone sarcomas; however, of note, these recommendations did not focus specifically on retroperitoneal lesions [24]. In this study, the diagnostic yield (total number of biopsies that yield a diagnosis divided by total number of biopsies) was 77% for all lesions and there were no differences in yield according to needle gauge or imaging modality. This yield is relatively low when compared to studies in other tissues such as breast (100%) and musculoskeletal tumors (91%) [25,26]. Nonetheless, it is comparable to previous studies of retroperitoneal sarcoma (72% and 82% yield) and a study on chest wall sarcoma biopsies (70% yield) [23,27,28]. The gap in the literature pertaining to biopsy of retroperitoneal sarcoma has therefore led our group to initiate a quality improvement audit of our tertiary centre.

OUR RESEARCH

As discussed, there are clear benefits to achieving histological diagnosis through biopsy of suspected retroperitoneal sarcomas when determining treatment plan, and these benefits favour patient safety and quality care improvement. That being said, no studies to date have examined the optimal method and parameters for sampling a suspected soft-tissue sarcoma originating in the retroperitoneum. Consequently, there is little literature to guide the clinician on the best practice for maximizing yield while minimizing risk of patient complications.

Our current research seeks to address this gap to provide guidelines for the safe and effective biopsy of retroperitoneal lesions. As retroperitoneal sarcomas are rare, we have collaborated with Mount Sinai Hospital in Toronto, a Cancer Care Ontario-designated Sarcoma centre, to obtain a large/representative sample size to retrospectively examine biopsy parameters of patients referred to our centres for suspected retroperitoneal sarcoma. The patient population in our study includes almost 400 patients who have undergone biopsy for suspected sarcoma at Mount Sinai Hospital or The Ottawa Hospital between 1999 and 2015. Patients were included in the retrospective review if they presented with a retroperitoneal mass, were older than 18 years of age and had a biopsy of the lesion. Patients were excluded if their lesion was suspected to be intra-peritoneal in origin or was not suspected to be a sarcoma. Pathology reports, diagnostic imaging study reports, and clinical consult and progress notes were used to record biopsy information for each patient in the study. These included lesion location, lesion composition based on diagnostic imaging, size of tumor, image-guidance modality for biopsy, biopsy needle gauge, number of specimens sent for pathological analysis, longest length of biopsy specimens, location where biopsy was performed (i.e. tertiary or primary care center), diagnosis at biopsy, whether the lesion is a recurrence or primary tumor, complications secondary to biopsy procedure, and final diagnosis based on post-operative pathology. Standard demographics were also collected. As mentioned above, we have previously investigated needle tract seeding in our patient cohort, therefore this data was not included in our current study.

Our next step is comparing diagnostic yield based on biopsy type (fine needle versus core), gauge size, number of passes, specimen size, and image-guidance modality. Most significantly, we are comparing the pathological diagnosis from the biopsy with the pathological diagnosis obtained from the final surgical specimen in order to calculate diagnostic accuracy. Our patient sample size is one of the largest of studies concerning retroperitoneal lesions; hopefully, this will provide support for our recommendations. This study is currently at the data analysis stage and the results will be reported in a future manuscript. The main goal of our study is to guide institutions towards standardization of retroperitoneal lesion biopsy protocols where quality and patient safety are prioritized.

CONCLUSION

Due to their rarity, little evidence-based data is available for surgical oncologists treating retroperitoneal sarcomas to base proper management of these tumours. Furthermore, due to past controversy over the safety of biopsy of these masses, there are no agreed upon and validated guidelines to direct sampling of these lesions. Specialized centres across the world have come together to form the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG) in order to gather maximum patient data of a rare disease, create guidelines on the diagnosis and surgical management of these tumours, and disseminate knowledge to physicians treating this disease. As a tertiary centre for sarcoma treatment, and as Dr. Carolyn Nessim is an active member of the TARPSWG, our overall goal as a centre is to contribute to the output of evidence-based data that can be trusted by clinicians to guide biopsy procedures in their practice. This will ultimately lead to consistent, quality, and safe care for all patients presenting with these lesions.

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REFERENCES

1. Al-Absi E, Farrokhyar F, Sharma R, et al. A systematic review and meta-analysis of oncologic outcomes of pre- versus postoperative radiation in localized resectable soft-tissue sarcoma. Ann Surg Oncol. 2010;17(5):1367–74.
2. Van Roggen JFG, Hogendoorn PCW. Soft tissue tumours of the retroperitoneum. Sarcoma. 2000;4:17–26.
3. Strauss DC, Hayes AJ, Thomas JM. Retroperitoneal tumours: Review of management. Ann R Coll Surg Engl. 2011;93(4):275–80.
4. Canadian Cancer Society. Canadian Cancer Statistics 2016 [Internet]. Updated Oct. 2016 [cited 2017 Mar 7]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer information/cancer 101/Canadian cancer statistics/Canadian-Cancer-Statistics-2016-EN.pdf?la=en
5. Solla JA, Reed K. Primary retroperitoneal sarcomas. Am J Surg. 1986;152(5):496–8.
6. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg. 1998;228(3):355–65.
7. Windham TC, Pisters PWT. Retroperitoneal sarcomas. Cancer Control. 2005;12(1):36–43.
8. Potter DA, Glenn J, Kinsella T, et al. Patterns of recurrence in patients with high-grade soft-tissue sarcomas. J Clin Oncol. 1985;3(3):353–66.
9. Mazeron JJ, Suit HD. Lymph nodes as sites of metastases from sarcomas of soft tissue. Cancer. 1987;60(8):1800–8.
10. Blazer III DG, Sabel MS, Sondak VK. Is there a role for sentinel lymph node biopsy in the management of sarcoma? Surg Oncol. 2003;12(3):201–6.
11. European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Supplement 3):iii102-iii112.
12. Karakousis CP, Gerstenbluth R, Kontzoglou K, Driscoll DL. Retroperitoneal Sarcomas and Their Management. Arch Surg. 1995;130:1104–9.
13. Francis IR, Cohan RH, Varma DG, Sondak VK. Retroperitoneal sarcomas. Cancer Imaging. 2005;5:89–94.
14. Arca MJ, Sondak VK, Chang AE. Diagnostic procedures and pretreatment evaluation of soft tissue sarcomas. Semin Surg Oncol. 1994;10(5):323–31.
15. Berger-Richardson D, Swallow CJ. Needle tract seeding after percutaneous biopsy of sarcoma: Risk/benefit considerations. Cancer. 2016.
16. Lahat G, Madewell JE, Anaya DA, et al. Computed tomography scan-driven selection of treatment for retroperitoneal liposarcoma histologic subtypes. Cancer. 2009;115(5):1081–90.
17. Pham V, Henderson-Jackson E, Doepker MP, et al. Practical Issues for Retroperitoneal Sarcoma. Cancer Control 2016;23(3):249-64.
18. Trans-Atlantic RPS Working Group. Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach From the Trans-Atlantic RPS Working Group. Ann Surg Oncol. 2015;22(1):256–63.
19. Miah AB, Hannay J, Benson C, et al. Optimal management of primary retroperitoneal sarcoma: an update. Expert Rev Anticancer Ther. 2014;14(5):565–79.
20. Strauss DC, Hayes AJ, Thomas JM. Preoperative core needle biopsy is safe and does not affect oncological outcome in retroperitoneal sarcoma. CTOS 17th Annu Meet. 2012.
21. Wilkinson MJ, Martin JL, Khan AA, Hayes AJ, Thomas JM, Strauss DC. Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival. Ann Surg Oncol. 2015;22(3):853–8.
22. Berger-Richardson D, Nessim C, Burtenshaw S, Gladdy R, Gronchi, A, Fiore M SC. Early and Late Complications of Percutaneous Biopsy of Retroperitoneal Masses at Three Tertiary Sarcoma Centers. In: Society of Surgical Oncology. 2017.
23. Hwang SY, Warrier S, Thompson S, Davidson T, Yang JL, Crowe P. Safety and accuracy of core biopsy in retroperitoneal sarcomas. Asia Pac J Clin Oncol. 2016;12(1):e174–8.
24. Wu JS, Goldsmith JD, Horwich PJ, Shetty SK, Hochman MG. Bone and soft-tissue lesions: what factors affect diagnostic yield of image-guided core-needle biopsy? Radiology. 2008;248(3):962–70.
25. Fishman JE, Milikowski C, Ramsinghani R, Velasquez MV, Aviram G. US-guided core-needle biopsy of the breast: How many specimens are necessary? Radiology. 2003;226(3):779–82.
26. Carrino J, Khurana B, Ready J, Silverman S, Winalski C. Magnetic Resonance Imaging-Guided Percutaneous Biopsy of Musculoskeletal Lesions. J Bone Jt Surg Am. 2007;89(10):2179–87.
27. Kachroo P, Pak PS, Sandha HS, et al. Chest Wall Sarcomas are Accurately Diagnosed by Image-Guided Core Needle Biopsy. J Thorac Oncol. 2012;7(1):151–6.
28. van Dalen T, van Coevorden F, van Geel A, Hoekstra H, Hennipman A. A biopsy of a suspected soft tissue sarcoma in the retroperitoneal space; the diagnostic yield and the risk of contamination of the different procedures. Eur J Cancer. 2001;37:S84.

Continuous Quality Improvement in Orthopaedic Surgery: Improving Patient Experience, Safety and Outcomes

Kathleen Gartke, MD, FRCSC[1]; Darren M. Roffey, PhD[1,2]; Johanna Dobransky, MHK[1]; Frank Devine, MSc, PEng[3]; Sean Denroche, BSc[3]; Stephen P. Kingwell, MD, FRCSC[1]; Stephane Poitras, PT, PhD[1,4]; Paul E. Beaule, MD, FRCSC[1,2]

[1] Division of Orthopaedic Surgery, University of Ottawa
[2] Clinical Epidemiology Program, Ottawa Hospital Research Institute
[3] Faculty of Medicine, University of Ottawa
[4] School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa

ABSTRACT

As the demand for accountability and transparency surrounding the supply of increasingly expensive medical services grows, healthcare providers have put continuous quality improvement (CQI) programs in place to optimize care and improve efficiencies. CQI programs that rigorously evaluate healthcare services can lead to informed decisions about the direction of planned improvements through evolving knowledge translation. Successful end products may include better patient satisfaction, improved patient-reported outcomes, highly-efficient care pathways, and overall cost-savings. There are numerous steps involved in implementing CQI programs that require collaboration and cooperation from physicians, allied health care workers, support staff and hospital management in order to achieve desirable goals. The Division of Orthopaedic Surgery at The Ottawa Hospital (TOH) has initiated a CQI program which is designed as a classic Donabedian Construct with a triple aim framework of: 1. improving care, 2. improving patient experience, and 3. lowering cost. The development of our electronic CQI database will be a key component in the 5-year (2015-2020) Strategic Plan for the Division, and is in keeping with the goal of TOH becoming a top 10% performer in quality and safety of patient care in North America. The aim of this paper is to outline our compliance with the ongoing activities required to meet clearly delineated quality metrics, and the development of the many facets of our CQI program.

RÉSUMÉ

En réponse à la demande croissante de transparence et de responsabilité concernant les services de santé dispendieux, les fournisseurs de soins de santé ont mis sur pied des programmes d'amélioration continue de la qualité (ACQ) pour optimiser les soins et l'efficience. Les programmes d'ACQ qui évaluent rigoureusement les services de santé permettent des décisions plus éclairées quant aux améliorations à apporter, grâce au transfert de connaissances. Parmi les résultats positifs de ces programmes, on peut compter une plus grande satisfaction et une amélioration des résultats rapportés par les patients, des plans d'intervention particulièrement efficients, et une réduction des coûts. De nombreuses étapes dans la mise en place des programmes d'ACQ nécessitent une collaboration entre les médecins, le personnel de soutien, les gestionnaires de l'hôpital et les autres professionnels de la santé afin d'atteindre les objectifs désirés. La Division de chirurgie orthopédique de l'Hôpital d'Ottawa a lancé un programme d'ACQ conçu selon le modèle classique Donabedian, qui poursuit un triple objectif : 1. améliorer les soins, 2. améliorer l'expérience des patients, et 3. minimiser les coûts. La création d'une base de données électronique pour l'ACQ sera une composante clé du plan stratégique de 5 ans (2015-2020) de la Division, et se conforme à l'objectif de l'Hôpital d'Ottawa de devenir l'un des plus performants en Amérique du Nord, sur le plan de la qualité et de la sécurité des soins aux patients. Le but de cet article est de décrire brièvement le développement de nombreuses facettes de notre programme d'ACQ, et notre conformité aux normes de la qualité.

BACKGROUND

Canadian healthcare organizations have been interested in continuous quality improvement (CQI) since the 1990's when a survey indicated growing awareness of the philosophy and methods of CQI in an effort to improve patient experience and safety [1]. Successful CQI initiatives modelled from commercial industry have been designed to use a structured planning approach to evaluate current healthcare processes and improve upon them to achieve the desired goals and vision [2,3]. Many such frameworks implemented recently have curtailed rising costs and proven valuable at improving patient outcomes and satisfaction [1,4,5]. In Ontario, the need for quality improvement plans have now migrated into a formal commitment, aligned with system and provincial priorities [6] brought forward by the Health System Funding Reform of April 2012 as part of Ontario's Action Plan for Health Care.

Given this mandate, The Ottawa Hospital (TOH) has stated that it aims to maintain and improve patient care while operating with-

Keywords: Continuous Quality Improvement; Orthopaedic Surgery; Safety; Patient Reported Outcomes; Quality Metrics; Adverse Events

in a budget, leading to better patient experience, better quality healthcare at less cost, and healthier populations. In line with this initiative, the Division of Orthopaedic Surgery established a five year (2015-20) Strategic Plan in which a CQI program designed to improve the quality of care was to be implemented. The purpose of this paper is to provide an outline of the key components of our CQI program as well as review early challenges and progress thus far in its implementation.

Quality Improvement in Healthcare

CQI in the context of healthcare was originally promoted by Donabedian, Berwick, and Jencks and Wilensky and represents a systematic approach to making changes that lead to better patient outcomes and stronger health system performance [5]. While there is agreement from an industry point-of-view that quality embodies notions of efficiency, effectiveness, and consumer satisfaction, the fact remains that in healthcare, definitions of quality can be subjective [7,8]. According to the Institute of Medicine [9], quality healthcare should be: 1. safe, 2. effective, 3. patient-centered, 4. timely, 5. efficient, and 6. equitable. Importantly, quality does not necessarily improve by spending more money; in fact, quality could be a means to save money, as better coordinated care can lead to lower complication rates, shorter lengths of stay, reduced readmissions, and reduced use of health services after surgery [10]. Furthermore, technological advances make it possible for these improvements to be real and systematic, and can provide safer care with fewer errors and better adherence to proven best practices. Regardless of definition, with the increased attention focused on optimizing healthcare value and patient outcomes, quality improvement practices have become increasingly mainstream [11].

Quality Improvement in the Division of Orthopaedic Surgery at TOH

Over the last four years the Division of Orthopaedic Surgery at TOH has been engaged in numerous hospital-led quality initiatives, each of which has resulted in improvements at a variety of levels. With a focus on improving safety culture and integrating safety practices into clinical units, the Comprehensive Unit-Based Safety Program (CUSP) was developed to address patient risks identified by frontline providers and, with hospital executive support, optimize physician buy-in and implement a safety culture [12]. Surgical site infections (SSI) in both orthopedic and neurosurgical spine patients have been the primary focus of CUSP to date. Initiatives that have been disseminated hospital-wide include: 1. patient pre-warming and 2. intra-operative time-out for operative cases exceeding 4 hours; the latter consisting of antibiotic redosing, patient positioning check, wound irrigation, retractor repositioning, and surgeon glove change. Specific to spine patients, the increased utilization of tranexamic acid, standardization of post-operative dressings and the auditing of spine surgeons' infection-prevention strategies have also been addressed through this initiative. To monitor these changes, the National Surgical Quality Improvement Program (NSQIP) data set collected at TOH was used. Historical spine SSI rates reported as a requirement of TOH's NSQIP involvement, representing a 20% sample, were 4.0% and 5.3% for neurosurgical and orthopedic spine patients respectively from 2010-2015. As of January 2016, TOH has utilized the NSQIP procedure-targeted process for 100% sampling of targeted procedures, which include all spine cases. The resultant combined orthopedic and neurosurgical spine SSI rate of 2.4% provides a more accurate overall picture, making it easier to assess the success of interventions that have been put in place.

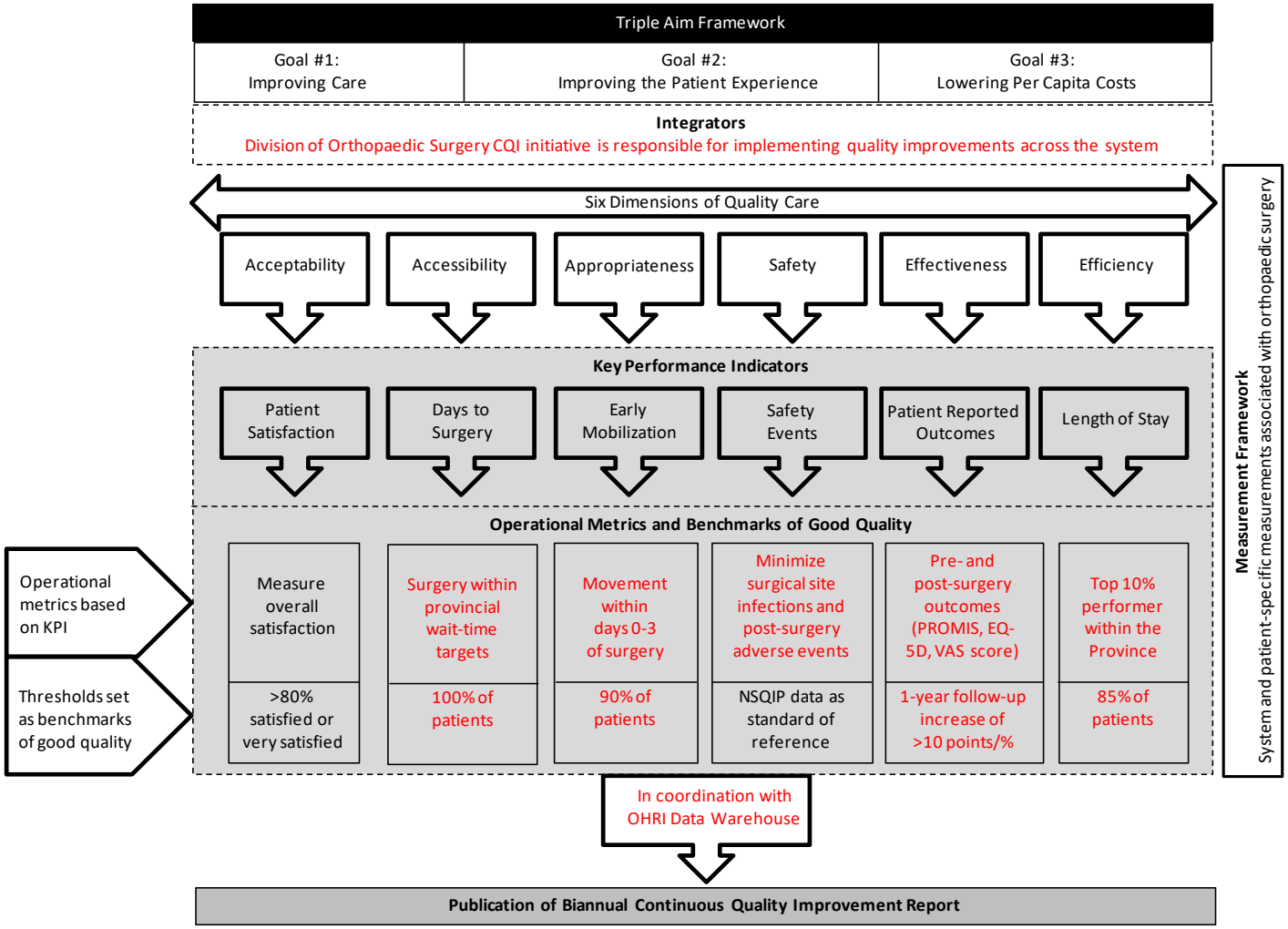
In addition, to improve patient safety as well as facilitate both physicians' and allied health engagement, the Patient Safety Learning System (PSLS) was introduced as a self-reporting tool available online through the hospital portal. A review of approximately 80 of the Division of Orthopaedic Surgery PSLS events was carried out between November 2015 and November 2016. The most common themes identified were: 1. inadvertent patient injury (at the time of surgery, during dressing changes), 2. positioning issues (excess pressure over time, sudden loss of support—occasionally leading to patient injury) and, 3. medication errors (incorrect, not ordered, records not completed).

However, there was a lack of coordination in connecting these initiatives, no grading for the severity of the events putting patient safety at risk, as well as limited physician engagement. Hence in 2016 we commenced documenting and requiring physicians to report adverse events (AEs), which are then analysed for themes and discussed with members of the Division of Orthopaedic Surgery as part of Morbidity and Mortality rounds for consideration of potential improvements at the Divisional level and within individual Clinical Practice Units (CPUs), which are subspecialty areas of the orthopaedic surgery umbrella. With regards to AE reporting, we have introduced the OrthoSAVES tool, which we previously validated against surgeon-driven reporting and manual chart reviews [13]. In total, from January 2016 to November 2016, 372 AEs were reported in 266 patients, with 106 patients reporting 2 or more AEs. AEs were graded based on the validated Clavien-Dindo Classification [14], originally adapted by Sink et al. in 2011 [15]. There were 266 Grade 1 or Grade 2 AEs, of which urinary tract infection (UTI) and delirium were most prevalent, and 53 Grade 3 AEs, of which SSIs were most common. In an effort to decrease our reported AEs, we have created a urology working group that will begin to implement the methods and protocols suggested by the Division of Urology with the aim of reducing UTI occurrence by a minimum of 50%. In addition, specific educational sessions and feedback to staff are now provided at monthly patient safety and CQI meetings and resident rounds.

We are currently working to have the reporting/monitoring of AEs reach a compliance rate of greater than 80%.

Electronic CQI Database for Healthcare Outcomes

As part of our Strategic Plan (2015-2020), we are developing our comprehensive Division-wide electronic CQI database [16]. To serve as the starting point for our quality improvement initiative, the Donabedian Construct [5,17] was utilized to distinguish among the following three aspects of quality in healthcare: 1. the structure of the health care system, 2. the processes of care, and 3. the outcomes of care. CQI starts by identifying areas of improvement using health care outcome indicators. To define these outcomes, the Triple Aim framework of patient health outcomes, the patient experience, and per capita costs was then filtered into the Six Dimensions of Quality Care. From there, assessable and operational quality metrics were outlined (**Figure 1**).



Note: The red font represents Division of Orthopaedic Surgery CQI Program elements.
KPI: Key Performance Indicator; EQ-5D: EuroQol 5 Dimension Quality of Life; VAS: Visual Analogue Scale; NSQIP: National Surgical Quality Improvement Program

Figure 1: Donabedian Construct Diagram (Adapted from [17]).

The core tenets of our electronic CQI database include: 1. the collection of data containing clinically relevant patient variables that allow assessment of clinical outcomes, 2. feedback of outcomes data to surgeons with risk adjustment and benchmarking of the data, and 3. implementation of appropriate interventions to promote reduction in wasteful and inefficient variation in care, while simultaneously improving processes and performance. Patient-centered outcomes typically include self-perceived quality of life, physical functioning and overall satisfaction with care and outcomes [18]. In order to improve outcomes, services provided and resources used also need to be recorded, analyzed and benchmarked in conjunction with the dynamics of the healthcare pathway in which patients interact. One recent success story in Canada with respect to integrating a CQI program for hip and knee replacement surgical care was presented by Marshall et al. [5]. Working collaboratively, multidisciplinary experts managed to embed the Triple Aim framework and six dimensions of quality care into everyday practices in clinics across Alberta. As of publication, 83% of surgeons were participating in the CQI program, representing 95% of the total volume of hip and knee surgeries. Biannual reports were also providing feedback to improve care processes, infrastructure planning, and patient outcomes.

In regards to our electronic CQI database, we have completed the design element and have started the implementation phase. Our CPUs have been developed and are both condition and anatomic specific: Foot and Ankle, Orthopaedic Oncology, Spine, Sports Medicine and Knee Preservation, Upper Extremity (Hand and Wrist; Shoulder and Elbow), Adult Reconstruction, and Trauma. Within every CPU, the initial focus will be to collect data on the five most prevalent and/or costly conditions (**Table 1**). For example, in the Foot and Ankle CPU, this will be: 1. Ankle Osteoarthritis; 2. Ankle Osteochondritis Dissecans; 3. Complex deformity (pes planus/pes cavus); 4. Achilles rupture and tendinopathies; and 5. Hallux disorders. Afflicted patients meeting entry criteria with one of these five conditions who require surgery will be enrolled into our electronic CQI database facilitated through a tailor-made software platform. From there, individual patients and healthcare performance will be assessed and followed during their journey at TOH in accordance with the detailed workflow diagrams set out in **Figures 2a-2d**.

When implementing such a large scale electronic CQI database, the time and personnel involvement is significant. This either has involved or will continue to require biweekly to weekly meetings with a large number of stakeholders including members of the Patient Safety and CQI committee; heads of the CPUs; orthopaedic surgeons; CQI assistants; research assistants and coordinators; orthopaedic administrators; orthopaedic clinic and ward clerks and nurses; and patients themselves. In addition, key members from the hospital administrative standpoint that have been involved and must be continually consulted include Contracting

Table 1: Clinical practice units in the Division of Orthopaedic Surgery at TOH and their top five conditions of interest.

Clinical Practice Unit	Top Conditions of Interest
Foot & Ankle	Ankle osteoarthritis Ankle osteochondritis dissecans Complex deformity Achilles rupture and tendinopathies Hallux valgus and osteoarthritis
Orthopaedic Oncology	Soft tissue sarcoma Bone sarcoma Metastatic bone disease Benign bone tumour Benign sarcoma
Spine	Cervical myelopathy/radiculopathy Lumbar spinal stenosis Lumbar disc herniation/radiculopathy Spondylolisthesis Scoliosis/Kyphosis
Sports Medicine & Knee Preservation	Meniscal Tear Ligament Tear Limb deformity Hip labral tear Articular cartilage injuries
Upper Extremity – Hand & Wrist	Scaphoid non-union Scapholunate advanced collapse Triangular fibrocartilage complex tear Scaphoid non-union advanced collapse Carpometacarpal osteoarthritis
Upper Extremity – Elbow & Shoulder	Shoulder Arthritis Shoulder Instability Rotator Cuff Tear Elbow arthritis Elbow contracture
Adult Reconstruction	Hip and knee arthritis Instability of hip and knee replacement Aseptic loosening of hip and knee replacement Septic failure of hip and knee replacement Peri-prosthetic fracture
Trauma	Distal radius fracture Tibial shaft fracture Proximal femur fracture Ankle fracture Acetabular and pelvic fractures

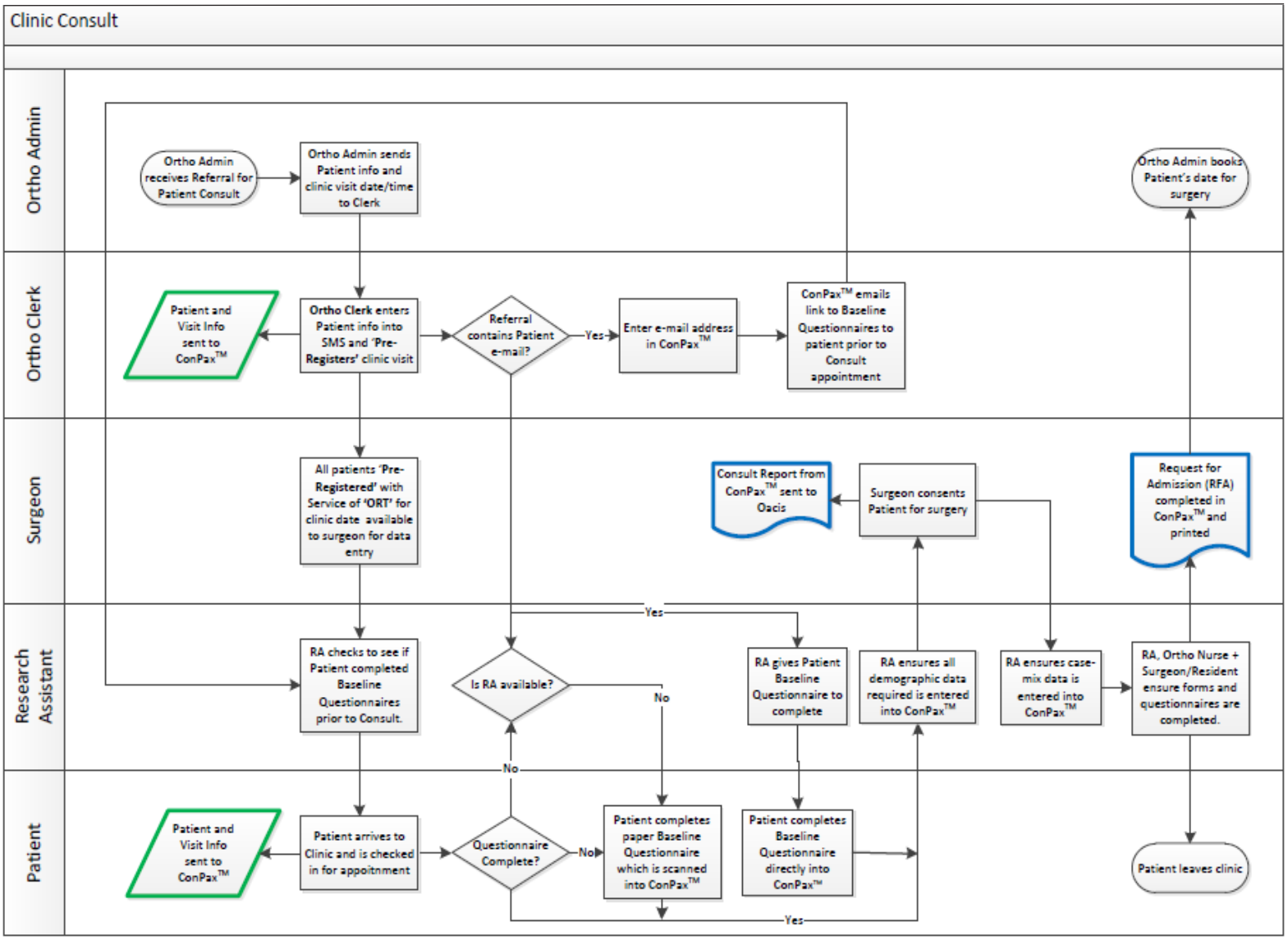


Figure 2a: Workflow of Orthopaedic CQI Program: Pre-operative Consultation Clinic Appointment.
SMS: Corporate SMS Registration System; RA: Research Assistant; ConPax: CQI Software Program; Oacis: TOH Electronic Medical Records

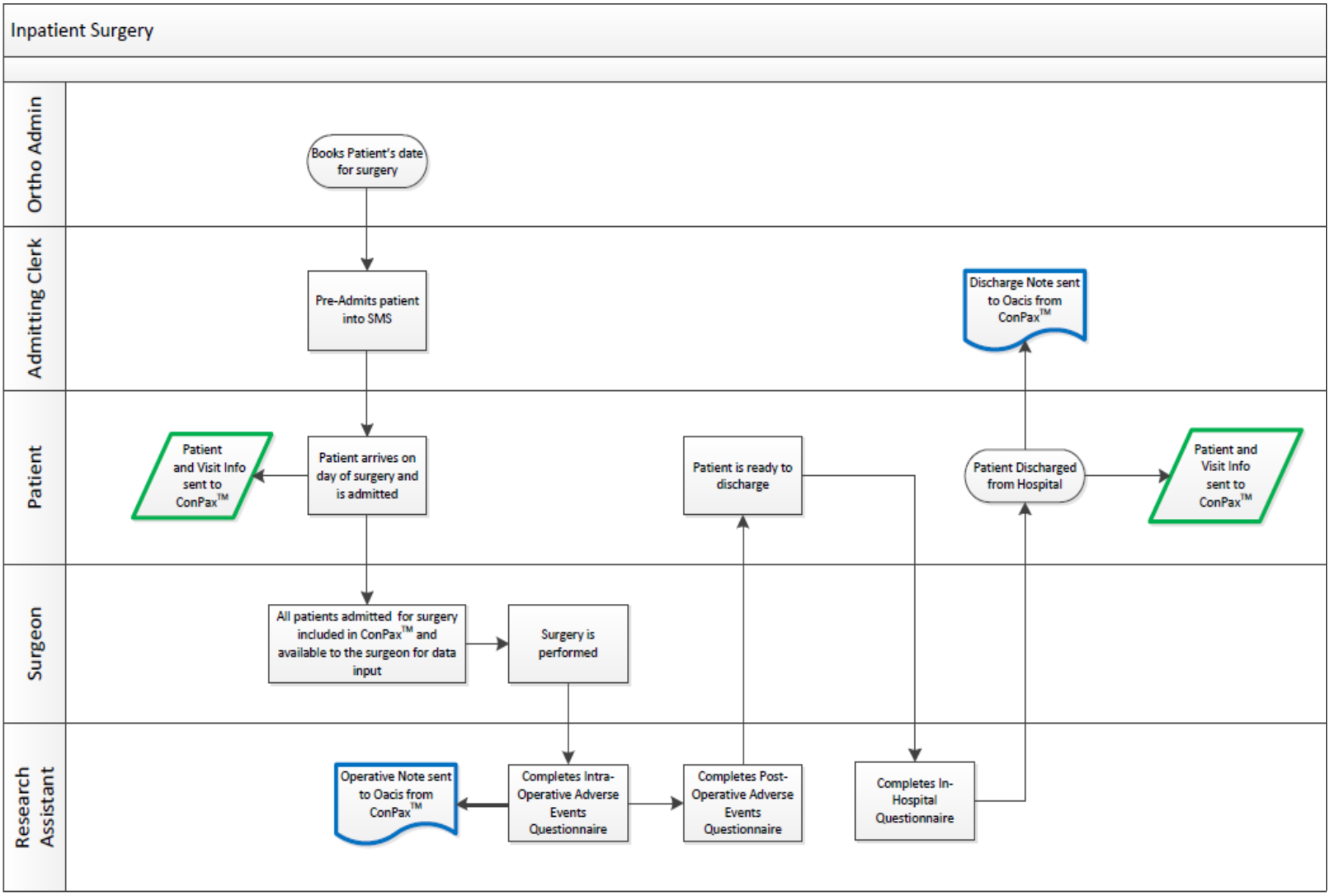


Figure 2b: Workflow of Orthopaedic CQI Program: Inpatient Surgery with Hospital Admittance.
SMS: Corporate SMS Registration System; ConPax: CQI Software Program; Oacis: TOH Electronic Medical Records

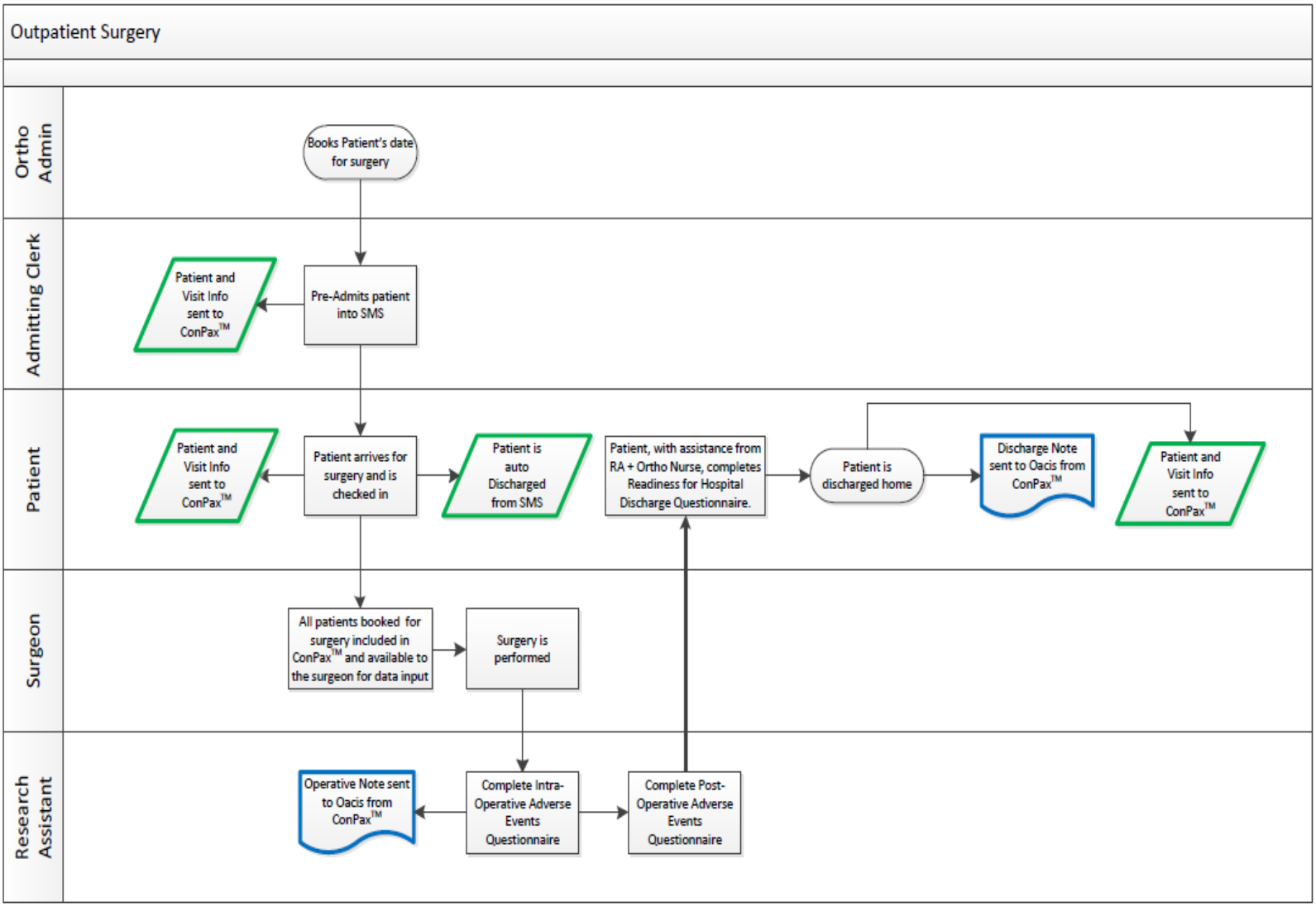


Figure 2c: Workflow of Orthopaedic CQI Program: Outpatient Surgery with Same-day Discharge.
SMS: Corporate SMS Registration System; RA: Research Assistant; ConPax: CQI Software Program; Oacis: TOH Electronic Medical Records

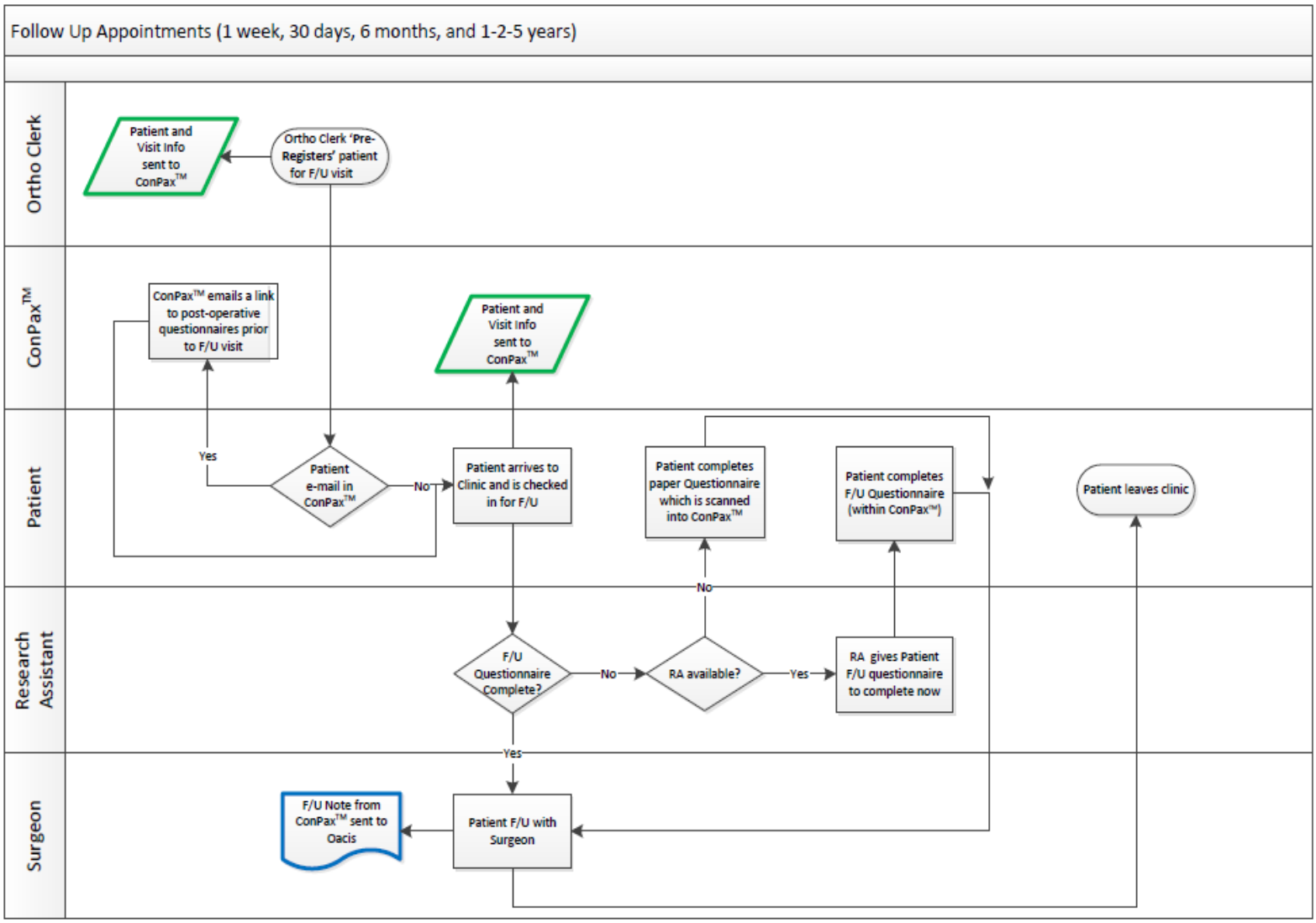


Figure 2d: Workflow of Orthopaedic CQI Program: Post-operative Follow-up Clinic Appointment.
SMS: Corporate SMS Registration System; RA: Research Assistant; ConPax: CQI Software Program; Oacis: TOH Electronic Medical Records; F/U: Follow-up

and Procurement; Information Services Steering Committee and Program Managers; and members of the Information Technology team. Finally, the electronic CQI database software platform must have the capacity to be tailored to the hospital IT system as well as each individual CPU.

At each stage of the respective workflow, data for CQI purposes will be collected and analyzed in order to produce quarterly reports designed to provide the Division of Orthopaedic Surgery with an overview of our performance, and indicators as to how to improve the quality of our medical care. Critical feedback from the reports will help to provide a more sensible distribution of tasks associated with data collection and data entry in order to enhance physician and staff engagement by limiting their time on keyboard while spending more time with their patients [19]. Of note, there is currently not enough evidence to be able to determine what incentive structure might "work" in a particular health-care system. Future efforts will necessitate the need for strong physician leadership and engagement in helping to ensure an optimal care team that is as patient-centered as possible. In that regards, gaining a better understanding of the challenges/barriers for physician engagement is a critical step when implementing a CQI program.

CQI Program: Studying Processes – Most Responsible Physician (Example Project)

In addition to obtaining valid patient outcome data, the assessment of health care processes is a critical aspect of any CQI program, where evaluation of health care services is necessary in order to identify and correct deficiencies and ultimately improve outcomes. A commonly documented deficiency lies in the communication between physicians and other healthcare providers. Breakdowns in communication have been cited as one of the leading causes of AEs that can threaten the safety of a patient [20-22]. Poor communication can lead to confusion about the identity of the most responsible physician (MRP). As explained by the Canadian Medical Protective Association, the MRP is "the physician who has overall responsibility for directing and coordinating the care and management of an individual patient at a specific point in time. They are also responsible for making a record of any interaction; furthermore, this record should be legible." [23]. Consequently, proper identification of the MRP is important to ensure that patients, their families and other healthcare personnel know who is caring for them, how they are responding to the medical treatment, and who is responsible for making critical decisions—sometimes on short notice in acute situations.

To address this critical issue, TOH implemented the Elizabeth and Matthew Policy in 2014 to outline the standard of communication and documentation concerning the MRP and patient care both for in-hospital and ambulatory care. Although the Elizabeth and Matthew Policy is local to TOH, other hospitals across Canada and the United States have similar policies outlining MRP expectations. In order to assess the effectiveness of this policy as well as determine the level of physician engagement or compliance, the Patient Safety and CQI committee set out to evaluate two key questions: 1. Does the MRP provide proper documentation of their encounters with a patient within 24 hours of admission, daily throughout the acute treatment phase, and document discharge instructions?, and 2. What is the accuracy of MRP identification? Findings from this study will be enacted upon in our CQI program in terms of physician identification and responsibility for data completion.

Table 2: Presence of notes, note legibility, and signature legibility at 24-hour post-admission and on post-operative days (POD) and at discharge (D/C).

Inpatient Time Period					
MRP only	24-hour note	POD 1	POD 2	POD 3	D/C
Presence of notes	62/320 (19.4%)	32/229 (14.0%)	11/156 (7.1%)	4/110 (3.6%)	23/320 (7.2%)
Note legibility	23/62 (37.1%)	2/32 (6.3%)	0/11 (0%)	0/4 (0%)	6/23 (26.1%)
Signature legibility	5/62 (8.1%)	0/32 (0%)	0/11 (0%)	0/4 (0%)	0/23 (0%)
MRP and Trainees	**24-hour note**	**POD 1**	**POD 2**	**POD 3**	**D/C**
Presence of notes	310/320 (96.9%)	209/229 (91.3%)	141/156 (90.4%)	101/110 (91.8%)	227/320 (86.6%)

MRP: most responsible physician; POD: post-operative day; D/C: discharge

Retrospective Chart Audit

A retrospective chart audit was completed for a random sample of 320 out of 1891 admitted elective orthopaedic surgery patients from January to December 2015. Two independent reviewers examined patient charts and documented presence of notes, note legibility, and signature legibility for eight orthopaedic MRPs within 24 hours of admission, during weekday hospitalization on post-operative days (POD) 1, 2, and 3, and prior to discharge (**Table 2**). Fewer than 20% of inpatients had notes written by the MRP in their chart during their inpatient course. When there were notes in the patient's chart, fewer than 40% were legible. Furthermore, less than 10% of signatures were legible. When resident, fellow, and medical student notes were considered as valid documentation, numbers improved dramatically: within 24 hours of admission, 96.9% of patients had a note in their chart, 91.3%, 90.4%, 91.8% had notes present at POD 1, 2, and 3 respectively, and 86.6% had notes at discharge. These findings are helpful in policy design as they question whether the Elizabeth and Matthew Policy should be modified to permit MRP counter-signature of notes written by trainees rather than those written by the MRP themselves (which are frequently illegible).

Prospective Real-time Audit

Two independent reviewers evaluated MRP identification in 190 patients between June and August 2016, by reviewing: 1. the chart binder label of the patient; 2. the white board; and 3. Oacis (TOH's electronic medical records). At first review after admission, the MRP was correctly identified 36.3%, 44.7%, and 93.2% of the time on the chart binder label, white board, and in Oacis, respectively. At review any time post-admission, the MRP was correctly identified 36.3%, 66.8%, and 97.4% of the time on the chart binder label, white board, and in Oacis, respectively (**Table 3**). Together, these results demonstrate that MRP identification can be problematic with multiple sites of recording, and that errors on chart binder labels and white boards can persist throughout the admission. Identification of MRP via chart binder label and the white board also highlighted that there was a significant learning curve in the first few months of implementing a new comprehensive orthopaedic service wherein all surgeries regardless of elective or emergency were converted under one MRP on a week-to-week basis.

Table 3: Correct identification of most-responsible physician (MRP) at first review after admission compared to at any time after admission on the orthopaedic surgery inpatient unit.

Correct Identification (%) at ay time after	
Source	Total
Chart Binder Label	69/190 (36.3%)
White Board	85/190 (44.7%)
Oacis	177/190 (93.2%)
Correct identification (%) at any time after	
Source	Total
Chart Binder Label	69/190 (36.3%)
White Board	127/190 (66.8%)
Oacis	185/190 (97.4%)

Oacis: TOH electronic medical records

These two set of results—retrospective chart audit vs. prospective real-time audit—provide key insights into a potential barrier for CQI program implementation. Physician engagement remains a challenge for proper documentation, as well as issues with processes within the institution which can put patient safety at risk in the acute setting.

FUTURE DIRECTIONS

Canadian physicians are becoming increasingly accountable to the public for both the cost and quality of the care they provide. All physicians, not just orthopaedic surgeons, must become active participants in the quality movement by understanding the basic principles of CQI and how they apply to patient care. The best chance of improving overall care is through the adoption of systems that improve coordination and continuity. The Division of Orthopaedic Surgery at TOH has been a leader in embracing CQI initiatives as a priority. Only through collaboration and integration can healthcare incorporate a culture for improving quality and patient safety.

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REFERENCES

1. Baker GR, Barnsley J, Murray M. Continuous quality improvement in Canadian health care organizations. Leadersh Health Serv. 1993;2(5):18-23.
2. Goldstone J. The role of quality assurance versus continuous quality improvement. J Vascular Surgery. 1998;28(2):378-80.
3. Health Information Technology Research Center (HITRC). Continuous Quality Improvement (CQI) Strategies to Optimize your Practice [Internet]; 2013 [cited 14 April 2017]. Available from: https://www.healthit.gov/sites/default/files/tools/nlc_continuousqualityimprovementprimer.pdf.
4. Frank C, Marshall D, Faris P, Smith C; Alberta Bone and Joint Health Institute. Essay for the CIHR/CMAJ award: improving access to hip and knee replacement and its quality by adopting a new model of care in Alberta. CMAJ. 2011;183(6):E347-50.
5. Marshall DA, Christiansen T, Smith C, et al. Continuous quality improvement program for hip and knee replacement. Am J Med Qual. 2015;30(5):425-31.

6. Health Quality Ontario. Quality Improvement Planning [Internet]. 2016 [cited 14 April 2017]. Available from: http://www.hqontario.ca/Quality-Improvement/Quality-Improvement-Plans/Quality-Improvement-Plan-Guidance.
7. Kahan B, Goodstadt M. Continuous quality improvement and health promotion: can CQI lead to better outcomes? Health Promot Int. 1999;14(1):83-91.
8. Health Quality Ontario. Quality Improvement Guide [Internet]. 2012 [cited 14 April 2017]. Available from: http://www.hqontario.ca/portals/0/documents/qi/qi-quality-improve-guide-2012-en.pdf.
9. Baker A. Crossing the quality chasm: A new health system for the 21st century. BMJ. 2001;323(7322):1192.
10. Saleh KJ, Bozic KJ, Graham DB, et al. Quality in orthopaedic surgery—an international perspective: AOA critical issues. J Bone Joint Surg Am. 2013;95(1):e3.
11. Pinney SJ, Page AE, Jevsevar DS, Bozic KJ. Current concept review: quality and process improvement in orthopedics. Orthop Res Rev. 2015;2016(8):1-11.
12. Wick EC, Hobson DB, Bennett JL, et al. Implementation of a surgical comprehensive unit-based safety program to reduce surgical site infections. J Am Coll Surg. 2012;215(2):193-200.
13. Chen BP, Garland K, Roffey DM, et al. Can Surgeons Adequately Capture Adverse Events Using the Spinal Adverse Events Severity System (SAVES) and OrthoSAVES? Clin Orthop Relat Res. 2016;475(1):253-60.
14. Sink EL, Leunig M, Zaltz I, et al. Reliability of a complication classification system for orthopaedic surgery. Clin Orthop Relat Res. 2012;470(8):2220-6.
15. Sink EL, Beaulé PE, Sucato D, et al. Multicenter study of complications following surgical dislocation of the hip. J Bone Joint Surg Am. 2011;93(12):1132-6.
16. Beaule PE, Roffey DM, Poitras S. Continuous quality improvement in orthopedic surgery: changes and implications with health system funding reform. Can J Surg. 2016;59(3):149-50.
17. Donabedian A. Evaluating the quality of medical care. 1966. Milbank Q. 2005;83(4):691-729.
18. International Consortium for Health Outcomes Measurement (ICHOM). Standard Set for Hip & Knee Osteoarthritis [Internet]. 2016 [cited 14 April 2017]. Available from: http://www.ichom.org/medical-conditions/hip-knee-osteoarthritis/.
19. Hailer NP. Orthopedic registry research - limitations and future perspectives. Acta Orthop. 2015;86(1):1-2.
20. Leonard M, Graham S, Bonacum D. The human factor: the critical importance of effective teamwork and communication in providing safe care. Qual Saf Health Care. 2004;13(Suppl 1):85-90.
21. Woolf SH, Kuzel AJ, Dovey SM, Phillips RL Jr. A string of mistakes: the importance of cascade analysis in describing, counting, and preventing medical errors. Ann Fam Med. 2004;2(4):317-26.
22. Colvin MO, Eisen LA, Gong MN. Improving the Patient Handoff Process in the Intensive Care Unit: Keys to Reducing Errors and Improving Outcomes. Semin Respir Crit Care Med. 2016;37(1):96-106.
23. CMPA. Who is the most responsible physician? Check your knowledge [Internet]. 2016 [cited 14 April 2017]. Available from: https://www.cmpa-acpm.ca/-/who-is-the-most-responsible-physician-check-your-knowledge.

Triple Negative Breast Cancer: A Review of Common Therapeutic Targets and Current Treatment Options

Daud Akhtar, BSc[1]; Ahsen Chaudhry, BSc[1]

[1] Faculty of Medicine, University of British of Columbia

ABSTRACT

Triple negative breast cancer (TNBC) is a subtype of breast cancer which lacks ER, PR, and HER2 expression. It is characterized by poor prognosis and resistance to standard treatment forms for breast cancer. Chemotherapy is still currently the core neo-adjuvant treatment option for patients with TNBC, although it has mixed levels of efficacy on overall survival and many serious side effects. Platinum-based therapies have been used to treat TNBC in conjunction with chemotherapy, but they are not a widely effective treatment due to the heterogeneity of TNBC. For this reason, other novel approaches, particularly those which target molecular components involved in TNBC pathogenesis, are being investigated. Angiogenesis inhibitors, which include monoclonal antibodies or small molecules that inhibit VEGF, have been shown to improve progression-free survival, but have not demonstrated an impact on overall survival. PARP enzyme inhibitors, when combined with chemotherapy and carboplatin for the treatment of TNBC, have demonstrated a significant reduction in risk progression and mortality. However, the majority of PARP inhibitors are still in trials and their effectiveness in clinical settings has yet to be determined. Additional proposed targets for directed therapy against TNBC include cell signalling pathways involving EGFR or PI3K. Overall, issues such as treatment resistance and side effects are important challenges that must be overcome in order to enable improvements in patient prognosis and clinical impact.

RÉSUMÉ

Le cancer du sein triple négatif (CSTN) est un sous-type de cancer du sein auquel il manque les récepteurs d'œstrogènes (ER), les récepteurs de progestérone (PR) et l'expression de HER2. Il est caractérisé par un pronostic défavorable et une résistance aux traitements standards du cancer du sein. À l'heure actuelle, la chimiothérapie est encore l'option principale de traitement néoadjuvant pour les patients ayant le CSTN, bien qu'elle ait des niveaux variés d'efficacité sur la survie globale, ainsi que de nombreux effets secondaires sérieux. Les thérapies à base de platine ont été utilisées pour traiter le CSTN en conjonction avec la chimiothérapie, mais elles ne sont pas très efficaces étant donné l'hétérogénéité du CSTN. En raison de cela, d'autres approches novatrices, particulièrement celles qui ciblent les composantes moléculaires impliquées dans la pathogenèse du CSTN, font actuellement l'objet d'enquêtes. Les inhibiteurs de l'angiogenèse, dont les anticorps monoclonaux ou les petites molécules inhibant le VEGF, ont démontré la capacité d'améliorer la survie sans progression de la maladie, mais n'ont pas démontré d'impact sur la survie globale. Les inhibiteurs d'enzymes PARP, lorsque combinés avec la chimiothérapie et le carboplatine pour le traitement du CSTN, ont démontré une réduction significative du risque de progression et de la mortalité. Toutefois, la majorité des inhibiteurs PARP subissent encore des essais et leur efficacité clinique reste à être déterminée. D'autres cibles suggérées pour la thérapie dirigée contre le CSTN incluent les voies de signalisation impliquant le EGFR ou le PI3K. Dans l'ensemble, des problèmes tels la résistance au traitement et les effets secondaires sont des défis importants qui doivent être surmontés afin de permettre des améliorations au niveau du pronostic du patient et de l'impact clinique.

INTRODUCTION

Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer in which tumours lack the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). TNBC can further be divided into basal-like and non-basal like breast cancer subtypes based on gene expression analysis. Approximately 80% of TNBC falls into the basal-like breast cancer category that lacks steroid receptor expression [1]. Since TNBC tumours lack ER, PR, and HER2, the main treatment forms for breast cancer, such as hormonal or HER2-directed therapy, are significantly less effective [2]. It is due to this key difference that TNBC is often characterised by poor prognosis, early relapse, and a significantly shorter overall survival rate following recurrences as compared to non-TNBC cancers [3].

Almost all of the classic hallmarks of cancer, including proliferation in the absence of growth signals, insensitivity to anti-growth factors, evasion of apoptosis, infinite replicative potential, invasion, metastasis, and sustained angiogenesis, are linked to abnormalities in the levels, functions, and interactions of proteins and signalling pathways [4]. Recent advancements in technology and biochemical research have identified a number of key proteins and pathways that could be potential therapeutic targets

Keywords: TNBC; Breast Cancer; Platinum Agents; PARP Inhibitors; Angiogenesis

in TNBC. Moreover, the heterogeneity of TNBC has fostered the development of personalized forms of treatment that can target the unique tumour phenotypes of individual patients. This review will outline the major concepts and molecular targets of TNBC, the existing treatment options, and the novel technologies that are being explored as future treatments.

THERAPEUTIC TARGETS IN TNBC

Receptor Pathways

Pathways, such as the tyrosine kinase receptor pathway, play essential roles in initiating processes associated with cell survival and cell proliferation in breast and other epithelial tissues. In normal physiological settings, these pathways are tightly regulated. In TNBC, some pathways such as those involving insulin like-growth factor 1 receptor (IGF1-R), epidermal growth factor receptor (EGFR), rat sarcoma (RAS), phosphatidylinositol 3-kinase (PI3K), and angiogenesis are dysregulated and have become the subject of extensive examination in hopes of identifying novel therapeutics [5]. Most of these pathways involve receptors that have an extracellular ligand-binding region, a trans-membrane region, and a cytoplasmic tyrosine kinase-containing domain, which together function to activate downstream signalling mechanisms [6]. These receptor pathways can be aberrantly activated by a variety of mechanisms such as excessive ligand levels, gain- or loss-of-function mutations, overexpression with or without gene amplification, and gene rearrangements [7]. All of these mechanisms can result in inappropriate activation of the receptor pathways, which can result in cancerous phenotypes.

Epidermal Growth Factor Receptors

EGFRs are a family of growth factor receptors that include HER1 and HER2. Many cancers have mutations that cause overexpression of EGFR, which leads to dysfunctional kinase activity and excessive growth-stimulating secondary messenger activation. Such accelerated proliferation has been consistently linked to an increased risk of disease recurrence and overall shortened patient survival [8].

A pathway associated with EGFR is the IGF pathway, which activates pathways and oncogenic kinases such as PI3K. The triggering of such signalling cascade pathways amplifies IGF-1's effect as a potent mitogen. High levels of IGF-1 and IGF-1R have been observed in breast cancer. Its important pro-oncogenic role, therefore, highlights it as an important culprit in breast cancer growth [9]. The extensive crosstalk that occurs between the signalling pathways associated with IGF-1R and EGFRs support the combination of IGF-1R inhibitors with an anti-EGFR as an effective therapeutic strategy [10].

Phosphatidylinositol 3-Kinase (PI3K) Pathway

One of the oncogenic kinase pathways that can be activated by IGF-1 is the PI3K/Protein Kinase B (AKT) central signalling pathway, which is downstream of many receptor tyrosine kinases. These tyrosine kinases regulate cell growth and proliferation by dephosphorylating PI3K. The phosphorylated PI3K plays a role in activating other oncogenic kinases including AKT1, AKT2, and AKT3 [11]. In many breast cancers, including TNBC, the catalytic domain involved in dephosphorylating PI3K is mutated or underexpressed by methylation, which prevents PI3K dephosphorylation and results in its constitutive activation [11]. Such activation has downstream effects on the mechanistic target of rapamycin (mTOR) complex, which mediates cancerous phenotypes through the suppression of cap-dependant translation inhibitors [12]. This role of the PI3K pathway in breast cancer pathogenesis therefore supports it as another critical target in TNBC cancer therapy.

Angiogenesis

In conjunction with the aberrant activation of signalling pathways, an equally important process in the progression of cancer is the recruitment of blood vessels. Angiogenesis is the process of vessel formation during physiological events such as wound healing or pregnancy. When dysregulated however, angiogenesis has been shown to play a role in tumour growth and spreading and is essential for cancer progression and dissemination [13]. Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGF-R) are the primary proteins responsible for the stimulation of angiogenesis. They play a role in regulating endothelial growth and blood vessel formation by stimulating cellular responses through tyrosine kinase receptor binding (VEGFRs) on the cell surface of breast cancer cells [13]. High levels of VEGF expression correspond to cancers that are fast growing and able to metastasize, and thus VEGF has been implicated with poor prognosis in breast cancer [14,15]. For these reasons, VEGF has been suggested as a suitable target for molecular therapy.

OVERVIEW OF TREATMENT FOR TNBC

Chemotherapy remains the core neoadjuvant treatment option for patients with TNBC. Due to the aggressive nature of TNBC, however, chemotherapeutical treatment has mixed levels of efficiency and often results in poor outcomes for patients, along with many debilitating side effects and cytotoxicity [2]. Symptoms associated with chemotherapy include vomiting, nausea, diarrhoea, fatigue, anemia, peripheral and central neuropathy, and weight changes. For this reason, identifying correct subtypes of TNBC using specific biomarkers and recognizing possible target options is an important challenge in TNBC treatment. Tumor suppressor genes, DNA repair enzymes, and other molecular path-

ways involved in cancerous phenotypes have been identified as biomarkers that could be used to develop personalized molecular targets for patients with TNBC [13,16]. The main treatment types which currently exist include platinum-based agents, angiogenesis inhibitors, and poly (ADP-ribose) polymerase (PARP) inhibitors.

Platinum-Based Agents

Platinum drugs are responsible for causing cell death by forming chemical cross-links with DNA. These cross-links disrupt essential processes such as DNA replication and transcription that are fundamental for cell growth [17]. Cisplatin, introduced approximately 20 years ago, was the first platinum analogue and is still in use today. They play an important role in the treatment of certain subsets of breast cancer such as TNBC [17]. However, platinum-based drugs are toxic and can be detrimental to nerve and kidney function [18]. Side effects associated with platinating agents include ototoxicity, peripheral neuropathy, myelosuppression, and nephrotoxicity [18]. Another important therapeutic hurdle associated with platinum-based therapy is the formation of platinum resistance in tumours [16]. Nevertheless, outcomes for platinum-containing agents have shown promise when combined with other targeted agents such as bevacizumab, iniparib, and erlotinib. A randomized phase II trial demonstrated promising overall progression-free survival response rates (17% versus 6%) when carboplatin was added to single-agent cetuximab in neo-adjuvant advanced TNBC patients [19]. Overall, while platinum-based therapy is not an effective targeted treatment approach due to the heterogeneity of TNBC, it has been shown to be an important component of adjunct/combination therapies [19].

Angiogenesis Inhibitors

Angiogenesis is an important factor in the growth and spread of cancer. It provides cancerous cells a pathway by which they are able to metastasize and a source of nutrients with which to grow. Specific targeting, in the case of angiogenesis, revolves around anti-VEGF therapy [14,15].

Currently, monoclonal antibodies such as bevacizumab or small molecules that inhibit tyrosine kinases are being explored as a novel approach to TNBC treatment. Angiogenesis inhibitors such as bevacizumab have been shown to improve progression-free survival in aggressive breast cancers. Specifically, a meta-analysis of three phase 3 trials demonstrated that bevacizumab, when used in conjunction with chemotherapy, can increase the median progression-free survival (8.1 months) as compared to those with chemotherapy alone (5.4 months) [20]. However, studies that have measured overall survival response have failed to detect significant improvements upon usage of anti-angiogenic treatments [21].

There are several limitations and concerns regarding the usage of angiogenesis inhibitors. Recent research has demonstrated an increased risk of bleeding complications such as epistaxis, hemoptysis, gastrointestinal bleeding, and thrombotic events with the use of bevacizumab [22]. Additionally, studies in mouse models have shown that VEGF inhibitors may concomitantly promote invasiveness and metastasis of tumours [23]. One plausible mechanism is tumour hypoxia: the more proficient an angiogenic factor is, the more effectively anti-angiogenic therapy will prevent tumour vessel formation and result in conditions that are hypoxic. This may create a selective pressure on tumour cells to acquire resistance to hypoxic conditions through the process of dedifferentiation, resulting in more aggressive and metastatic cells that are less sensitive to anti-angiogenic treatment [23]. Additionally, tumours may be able to escape such hypoxic conditions by undergoing invasive epithelial mesenchymal transition (EMT). Currently, due to the lack of any substantial improvement in the overall survival rate of patients with TNBC and the side effect profile that has emerged, angiogenesis inhibitors are not administered in adjuvant or metastatic settings.

Poly (ADP-Ribose) Polymerase (PARP) Inhibition

PARP is a DNA-repair enzyme involved in initiating DNA repair by binding to areas where DNA strand breakage has occurred. PARP uses nicotinamide adenine dinucleotide (NAD)+ as a substrate to generate ADP-ribose polymers, which play a role in initiating a signal to recruit other cellular proteins and factors that mediate an anti-recombinogenic effect [24]. This prevents inappropriate recombination of homologous DNA [24] and control of the homologous repair response, which is important in double-stranded break repair. For these reasons, it is a possible target in cancer treatment [25].

PARP inhibitors work by competitively blocking the catalytic domain of the PARP enzyme [25]. PARP inhibition has been shown to be a thousand times more toxic to cancer cells than normal cells, indicating high amounts of specificity [25]. This is most likely because PARP inhibitors exploit tumour cells' defect in homologous recombination. Normal cells can use homologous recombination for repair of double-stranded DNA damage to ensure survival [25]. Some tumours however, lose this ability and ultimately die if a serious mutation occurs which would require homologous recombination repair [25]. For this reason, PARP inhibitors are believed to sensitize cells to DNA-damaging agents by preventing the repair of lethal DNA lesions. PARP inhibitors have a similar side effect profile to other drugs consisting of nausea, vomiting, diarrhoea, and weight loss.

Recent Phase I and II studies that examined the PARP inhibitors

olaparib and veliparib have shown encouraging results in breast cancer, including TNBC, with regards to progression-free survival [24,26]. Furthermore, the PARP inhibitor iniparib, when combined with chemotherapy and carboplatin for the treatment of TNBC, demonstrated a 41% reduction in risk progression and a 43% reduction in mortality with a minimal increase in toxicity [24,27]. As with other targeted therapies, cancers can develop resistance to PARP inhibitors, which can limit their clinical effectives and utility [28]. Another concern with regards to PARP inhibitors is their ability to increase the risk of developing new primary malignancies due to their DNA-damaging mechanism of action [27]. Such findings have raised concern, and have emphasized the need to proceed with caution for use in adjuvant settings until more research is done to confirm their utility and safety.

CONCLUSION

TNBC is a subtype of breast cancer that is associated with poor prognosis and is resistant to the main forms of breast cancer treatment. Molecular therapeutics such as platinating agents, angiogenesis inhibitors, and PARP inhibitors have been suggested as possible solutions to the challenges facing TNBC treatment. TNBCs appear to be responsive to current neoadjuvant chemotherapeutic treatments in combination with platinum agents, yet there is still not enough evidence to support their use as a primary treatment. PARP inhibitors and angiogenesis inhibitors are promising novel therapeutic modalities, but several concerns over side effect profiles and efficacy remain to be resolved. Additionally, research is being undertaken to discover biomarkers that can aid in classifying the different sub-types of TNBC, thereby enabling specific targeting for the unique phenotypes of each individual patient. Advances in gene therapy and the use of genetic modification may also be future therapeutic modalities for targeted treatment of TNBC tumour cells. Overcoming the barriers associated with current TNBC treatment forms, particularly resistance, side effects, and efficacy, are important challenges that will enable improvements in patient prognosis and clinical impact.

CONFLICT OF INTERESTS

All authors have no conflict of interests to declare.

REFERENCES

1. Brouckaert O, Wildiers H, Floris G, Neven P. Update on triple-negative breast cancer: prognosis and management strategies. Int J Womens Heal. 2012;4:511-20.
2. Foulkes WD, Smith IE, Reis-filho JS. Triple-Negative Breast Cancer. 2010 p. 1938-48.
3. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429-34.
4. Tsuruo T, Naito M, Tomida A, Fujita N, Mashima T, Sakamoto H, et al. Molecular targeting therapy of cancer: drug resistance, apoptosis and survival signal. Cancer Sci. 2003;94(1):15-21.
5. Sawyers C. Targeted cancer therapy. Nature. 2004;432(7015):294-7.
6. Siegfried Z, Bonomi S, Ghigna C, Karni R. Regulation of the Ras-MAPK and PI3K-mTOR signalling pathways by alternative splicing in cancer. International Journal of Cell Biology. 2013;568931.
7. Chalhoub N, Baker SJ. PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol. 2009;4(1):127-50.
8. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, Mcguire WL. Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene. Science. 1987;235(4785):177-82
9. LeRoith D, Roberts CT. The insulin-like growth factor system and cancer. Cancer Letters. 2003;195(2):127-37.
10. Bachman KE, Argani P, Samuels Y, Silliman N, Ptak J, Szabo S, et al. The PIK-3CA gene is mutated with high frequency in human breast cancers. Cancer Biol Ther. 2004;3(8):772-5.
11. deGraffenried LA, Fulcher L, Friedrichs WE, Grünwald V, Ray RB, Hidalgo M. Reduced PTEN expression in breast cancer cells confers susceptibility to inhibitors of the PI3 kinase/Akt pathway. Ann Oncol. 2004;15(10):1510-6.
12. Fingar DC, Blenis J. Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. Oncogene. 2004;23(18):3151-71.
13. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144(5):646-74.
14. Loges S, Mazzone M, Hohensinner P, Carmeliet P. Silencing or Fueling Metastasis with VEGF Inhibitors: Antiangiogenesis Revisited. Cancer Cell. 2009;15(3):167-70.
15. Ebos JML, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis. Cancer Cell. 2009;15(3):232-9.
16. Bosch A, Eroles P, Zaragoza R, Vina JR, Lluch A. Triple-negative breast cancer: molecular features, pathogenesis, treatment and current lines of research. Cancer Treat Rev. 2010;36(3):206-15.
17. Venkitaraman R. Triple-negative/basal-like breast cancer: clinical, pathologic and molecular features. Expert Rev Anticancer Ther. 2010;10(2):199-207.
18. Staudacher L, Cottu PH, Diéras V, Vincent-Salomon A, Guilhaume MN, Escalup L, et al. Platinum-based chemotherapy in metastatic triple-negative breast cancer: The Institut Curie experience. Ann Oncol. 2011;22(4):848-56.
19. Gelmon K, Dent R, Mackey JR, Laing K, Mcleod D, Verma S. Targeting triple-negative breast cancer: Optimising therapeutic outcomes. Ann Oncol. 2012;23(9):2223-34.
20. O'Shaughnessy J, Miles D, Gray RJ, Dieras V, Perez E a, Zon R, et al. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). J Clin Oncol. 2010;28(15):2-4.
21. Rugo H. Inhibiting Angiogenesis in Breast Cancer: The Beginning of the End or the End of the Beginning. J Clin Oncol. 2012;30(9):898-901.
22. Elice F, Rodeghiero F. PL-09 side effects of anti-angiogenic drugs. In: Thrombosis Research. 2012.
23. Pàez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Viñals F, et al. Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis. Cancer Cell. 2009;15(3):220-31.
24. Sandhu SK, Yap TA, de Bono JS. Poly(ADP-ribose) polymerase inhibitors in cancer treatment: a clinical perspective. Eur J Cancer. 2010;46(1):9-20.
25. Lord CJ, Ashworth A. Targeted therapy for cancer using PARP inhibitors. Curr Opin Pharmacol. 2008;8(4):363-9.
26. Chuang HC, Kapuriya N, Kulp SK, Chen CS, Shapiro CL. Differential anti-proliferative activities of poly(ADP-ribose) polymerase (PARP) inhibitors in triple-negative breast cancer cells. Breast Cancer Res Treat. 2012;134(2):649-59.
27. Benafif S, Hall M. An update on PARP inhibitors for the treatment of cancer. Onco Targets Ther. 2015;8:519-28.
28. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med. 2015;13(1):188.

Extensive Chemical Burns in a Child from Misuse of Cantharidin: A Case Report

Chloé Ward, MD[1], Jiyeh Joo, BHSc[2], Michele Ramien, MD[1], Yvonne Ying, MD[3]

[1] Division of Dermatology, Department of Medicine, University of Ottawa and The Ottawa Hospital
[2] Faculty of Medicine, University of Ottawa
[3] Division of Paediatric Plastic Surgery, Department of Surgery University of Ottawa and The Ottawa Hospital, Children's Hospital of Eastern Ontario

ABSTRACT

Molluscum contagiosum (MC) is typically a benign and self-limited viral infection affecting the skin. When treatment of MC is requested, application of cantharidin in a physician's office is generally a safe, effective and commonly used treatment option for MC. Its misuse, however, can result in rare but significant adverse outcomes. This case report details an unfortunate incident of a child who developed a severe chemical burn as a result of misuse of Cantharidin 1% – Podophyllin – Salicylic Acid (Canthacur-PS) for the treatment of MC. Furthermore, it highlights the importance of physician familiarity with the poxvirus infection, the indications to treat MC in immunocompetent children, and the various treatment options, including the safe administration and potential complications of cantharidin. In children, cantharidin can easily and safely be applied to lesions in a non-traumatic and controlled manner in the physician's office. Caregiver education on the post-treatment management and early signs of potential complications may also prevent similar adverse outcomes from cantharidin misuse.

RÉSUMÉ

Le molluscum contagiosum (MC) est une infection virale généralement bénigne et spontanément résolutive affectant la peau. L'application de cantharidine dans un cabinet de médecin est une option thérapeutique sécuritaire, efficace et couramment utilisée pour traiter le MC. Toutefois, son mauvais usage peut entraîner des effets indésirables rares, mais importants. Cette étude de cas décrit l'incident malheureux d'un enfant ayant développé une brûlure chimique sévère en réponse à un mauvais usage de Canthacur-PS, qui contient de la cantharidine 1 %, de la podophylline et de l'acide salicylique, pour le traitement du MC. En outre, elle met en évidence l'importance pour les médecins de bien connaître cette infection au poxvirus, les indications de traitement du MC chez les enfants immunocompétents, et les options de traitement disponibles, incluant l'administration sécuritaire et les complications possibles de la cantharidine. Chez les enfants, la cantharidine peut facilement être appliquée aux lésions de manière sécuritaire, contrôlée et non traumatique dans un cabinet de médecin. La formation des soignants sur la prise en charge post-traitement et les signes précurseurs de complications possibles à la suite d'un mauvais usage de la cantharidine pourrait également aider à prévenir des effets indésirables similaires.

Molluscum contagiosum (MC) is a common childhood mucocutaneous viral infection characterized by small, discrete, dome-shaped, umbilicated papule(s) [1]. It is caused by the MC virus, in the Poxviridae Molluscipox genus. The epidermis is commonly inoculated at sites of impaired skin barrier function from direct minor trauma, such as from scratching or shaving [2]. The disease predominantly affects immunocompetent children, but can be more extensive in the setting of immunosuppression. In adults, it is often sexually transmitted and immunocompromised individuals are more susceptible, most notably in the setting of human immunodeficiency virus infection. Reported prevalence of the disease varies widely across the literature. It is estimated that MC virus affects approximately 4.6% of children in the United States and its incidence has been rising since the 1960s [1].

In immunocompetent children, MC is benign and self-resolves within a few months to years without active treatment. At times, the lesions can be widespread, distressing to the patient- particularly when present on the face- and may be associated with a molluscum dermatitis, potentially exacerbating underlying atopic dermatitis. Following an inflammatory host immune response to virally infected lesions, patients can also develop an id reaction-like eruption of erythematous, pruritic papules on the extensors. Such symptomatic scenarios often warrant active treatment despite the benign and self-limiting nature of the poxvirus infection. When deciding on a treatment plan, patient preference along with the risks and benefits of each treatment option must be considered [1]. Treatment of MC is usually well tolerated and can effectively alleviate symptoms, limit spread, clear the infection, improve cosmetic appearance, reduce patient distress, prevent secondary bacterial infections, and help control underlying atopic dermatitis [3].

There are many different treatment options for MC, including

Keywords: Cantharidin; Canthacur; Molluscum Contagiosum; Chemical Burn; Adverse Effect

physical and ablative methods such as curettage, manual expression, cryotherapy, chemovesicants, keratolytics, immune modulators, and antiviral drugs [**Table 1**] [1]. In the pediatric population, cantharidin is a quick, non-traumatic, and effective option in the office setting [2]. When applied properly, it produces a moderately controlled but delayed blistering reaction, resulting in mild erythema, blistering and pain which self-resolves within a few days [2,4,5].

Herein, we report a rare adverse outcome of a severe chemical burn in a child as a result of inappropriate treatment of MC with Cantharidin 1% – Podophyllin – Salicylic Acid (Canthacur-PS). Awareness of the MC infection and the proper use of cantharidin can facilitate safe and effective treatment. Moreover, it can prevent similar adverse outcomes from the inappropriate use of cantharidin.

CASE PRESENTATION

A 5-year-old healthy female presented to the Emergency Department at the Children's Hospital of Eastern Ontario with extensive painful chemical burns on the abdomen and upper thigh. The patient had erroneously been prescribed cantharidin 1% – podophyllin – salicylic acid (Canthacur-PS®) for home-administration. The medication was liberally applied to MC and surrounding areas of normal skin. A second application was repeated within 24 hours. Subsequently, she developed several bullae on the abdomen and thigh that evolved into large erosions, including areas of full-thickness ulcers. The total affected area covered approximately 10% of the total body surface area. Regions of full thickness involvement were eventually excised and closed by a plastic surgeon [**Figure 1**]. Ultimately, the patient was left with extensive scarring over her abdomen and right thigh following application

Table 1: Treatment ladder for childhood molluscum contagiosum [10].

Therapeutic Option	Mechanism	Example (s)
No active treatment	In immunocompetent patients, lesions do resolve spontaneously due to body's host immune response. Associated risk of spreading, pruritus and/or dermatitis, especially in the setting of underlying atopic dermatitis.	
Physical therapy	Physical or ablative destruction of molluscum contagiosum.	Curettage Cryotherapy Electrodesiccation Manual extraction CO2 ablative laser Pulsed dye laser
Chemical agent	Chemically destroys or acts as an irritant to stimulate an immunologic response.-	Phenol Trichloroacetic acid Cantharidin Podophyllotoxin Salicylic acid gel Benzoyl peroxide Retinoic acid Potassium hydroxide
Immune modulator	Enhances immune function and stimlates the clearance of the poxvirus.	Imiquimod Cimetidine Candida antigen Diphencyprone
Antiviral agent	Direct antiviral effect as a nitric oxide donor.	Cidofovir (in HIV patients)

Note: Adapted from [1].

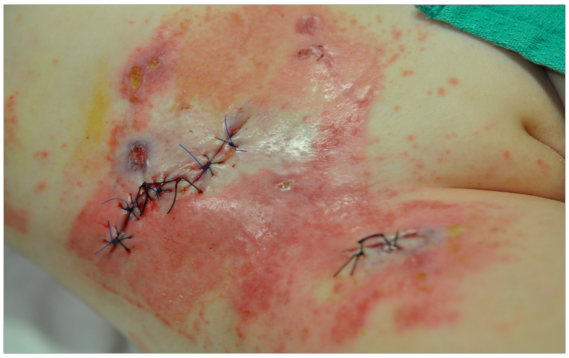

Figure 1: Right lower abdomen and upper thigh post-surgical resection of full thickness chemical burns from misuse of Cantha-cur-PS® for MC.

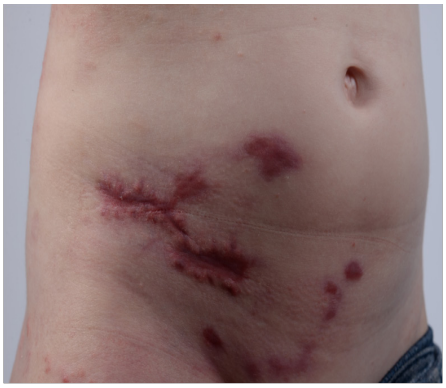

Figure 2: Right lower abdomen and upper thigh after a couple months with residual scarring.

of cantharidin 1% – podophyllin – salicylic acid for MC [**Figure 2**].

DISCUSSION

MC virus infection is very common amongst young children and easily spreads throughout the pediatric population [2]. It is a frequent reason to visit the family physician, pediatrician or dermatologist. In general, it is benign and self-limiting. Treatment is not always necessary but may be pursued in some cases for symptomatic relief, cosmesis, to limit spread, or to improve underlying eczema [3]. There are different options available for treatment of MC and the most appropriate therapeutic approach may vary depending on the clinical situation.

A recent trial comparing four recognized treatments of MC in a pediatric population (salicylic and lactic acid film, curettage, cantharidin, and imiquimod) found that curettage was the most effective treatment, with 80.6% of patients requiring only one visit to achieve clinical clearance. However, curettage can be challenging to perform in children as it requires the use of anesthesia and instrumentation, necessitating a process which is emotionally distressing for many children. In the study, cantharidin was found to be the second most effective treatment option in terms of overall patient and parent satisfaction [6]. In addition to its efficacy, cantharidin is a favourable option in children due to its quick, painless and controlled application in the office setting. Overall parental and physician satisfaction range from 60 to 90% with cantharidin in the Pediatric and Dermatology literature [4,7,8].

Cantharidin is a potent topical vesicant, derived from the "blister beetle," Lytta vesicatoria. The beetle-derived protein phosphatase inhibitor penetrates the epidermis, producing acantholysis and an intraepidermal blister [3,8]. When applied by an experienced physician, this controlled blistering reaction typically clears the infection safely, effectively, and without scarring [2,4,5]. However, adverse effects have been reported to range anywhere from 6-46 % [4]. These most commonly include pain, irritation, and inflammation from the blister [4]. The Food and Drug Administration also lists second- and third-degree burns and other extremely rare risks when cantharidin is applied with fatally high doses, ingested, or inhaled. Highly unlikely but reported risks include systemic toxicity, seizures, kidney damage, hypotension, hematuria, and cardiac abnormalities [9].

To our knowledge, there have been two case reports in the literature describing chemical burns secondary to cantharidin [10,11]. One additional case resulting in toxic shock syndrome from cantharidin has also been reported [12]. In general, cantharidin 0.7% is a safe treatment option for MC, but here we report a rare incident in which cantharidin 1% – podophyllin – salicylic acid was misused, resulting in full thickness chemical burns which could have been prevented. It emphasizes the importance that prescribing physicians should fully understand the product use before selecting it. Awareness of this rare complication, and other risks of cantharidin in treating MC, may foster safe use of the medication and prevent similar adverse events. In this case, three identifiable events may have prevented this serious adverse outcome.

First, the patient was prescribed Canthacur-PS® instead of plain Canthacur®. Cantharidin 0.7%, which is marketed in Canada as Canthacur® by Paladin Labs Inc., or CANTHARONE® by Dormer Laboratories Inc., is the standard of care when treating MC with cantharidin. Canthacur-PS® however, or similarly CANTHARONE® PLUS with podophyllin 2%, contains a higher concentration of cantharidin 1%, in addition to podophyllin 5% and salicylic acid 30%. The risk of excessive blistering, scarring and chemical cellulitis is higher with cantharidin 1% – podophyllin – salicylic acid than with cantharidin alone [7,8]. The risk was further increased with generous and repeated application to unaffected skin and

prolonged contact. Subsequently, Canthacur-PS® was dispensed at a pharmacy for self-administration against product monograph recommendations. Finally, the patient's guardian(s) failed to receive education on product use.

Under Health Canada regulation, the Natural Health Product monograph states it is designed strictly for physician application and under no circumstance should cantharidin 0.7% or cantharidin 1% – podophyllin – salicylic acid be dispensed or prescribed for patient administration [11]. At the first visit, the physician should assess sensitivity by treating only a few MC lesions, using a pointed wooden stick to apply a very small amount of solution to individual lesions. The solution should be left to dry uncovered and washed off within 4 to 6 hours with soap and water, or sooner if the patient develops discomfort. The treatment can be repeated in one to two weeks to more lesions using a similar protocol, once the inflammation has subsided [11].

In summary, this case highlights the importance of physician familiarity with cantharidin when selecting it as an active treatment for the common MC virus infection. Cantharidin 0.7% should be recognized as distinct from cantharidin 1% – podophyllin – salicylic acid and the latter should not be used to treat MC. Application to lesions should be restricted to the physician's office. And finally, all patients and their guardians should be told about the post-treatment management, potential side effects, and risks. Awareness of this serious adverse event and appropriate precautions can prevent future adverse outcomes, including chemical burns and scarring associated with the misuse of cantharidin.

KEY LEARNING POINTS

- Molluscum contagiosum is typically a benign and self-limited viral infection affecting the skin which does not always require active treatment, most notably in asymptomatic immunocompetent children.
- It presents as small, umbilicated, firm papules that can spread, become itchy, irritated and symptomatic for patients.
- Cantharidin can be a safe and effective treatment for MC but misuse can result in adverse reactions, including severe chemical burns.
- Cantharidin application should only be performed in a physician's office.
- Prescription and usage of Canthacur® and Canthecur-PS® should be clearly differentiated.

REFERENCES

1. Xiaoying C, Alex VA, Joachim J B. Molluscum contagiosum virus infection. The Lac Inf Disease. 2013;13(10):877-88.
2. Gottlieb S, Myskowski P. Molluscum contagiosum. Int J Dermatol. 1994;33(7):453-61.
3. Torbeck R, Pan M, de Moll E, Levitt J. Cantharidin: a comprehensive review of the clinical literature. Dermatol Online J. 2014;20(6):3.
4. Silverberg N. Pediatric molluscum contagiosum: optimal treatment strategies. Paediatr Drugs. 2003;5(8):505-12.
5. Cantharone. Dormer Products. Dormer – Cantharone Wart Removers [Internet]. Toronto (ON): Dormer Laboratories, Inc; 2015 [cited 2017 Jan 28]. Available from: http://www.dormer.com/Cantharone/AccDetail.aspx?ID=9001-975M
6. Peter L. Warts, molluscum and things that go bump on the skin: a practical guide. Arch Dis Child Educ Pract Ed. 2007;92(4):119-24.
7. Silverberg N, Sidbury R, Mancini A. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. J Am Acad Dermatol. 2000;43(3):503-7.
8. Coloe J, Morrell DS. Cantharidin use among pediatric dermatologists in the treatment of molluscum contagiosum. Pediatr Dermatol. 2009;26(4):405-8.
9. Cantharone. FDA Advisory Committees – Dockets [archival materials for years prior to 2009]. A. Ingredient Name: Cantharidin [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 1998 [cited 2017 Feb 10]. Available from: http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_02_18-BDL05.pdf
10. Hu L, Qiu XW. Deep chemical burn due to cantharidin: report of one case [Article in Chinese]. Di Yi Jun Yi Da Xue Xue Bao. 2005;25(12):1592.
11. Mjönes S. Cantharides poisoning with esophageal burns in a 2-year-old boy [Article in Swedish]. Lakartidningen. 1972;69(20):2364-5.
12. Langley JM, Soder CM, Schliever PM, Murray S. Case report: molluscum contagiosum. Toxic shock synderome following cantharidin treatment. Can Fam Physician. 2003;49(7):887-9.

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