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CHRONIC DISEASE

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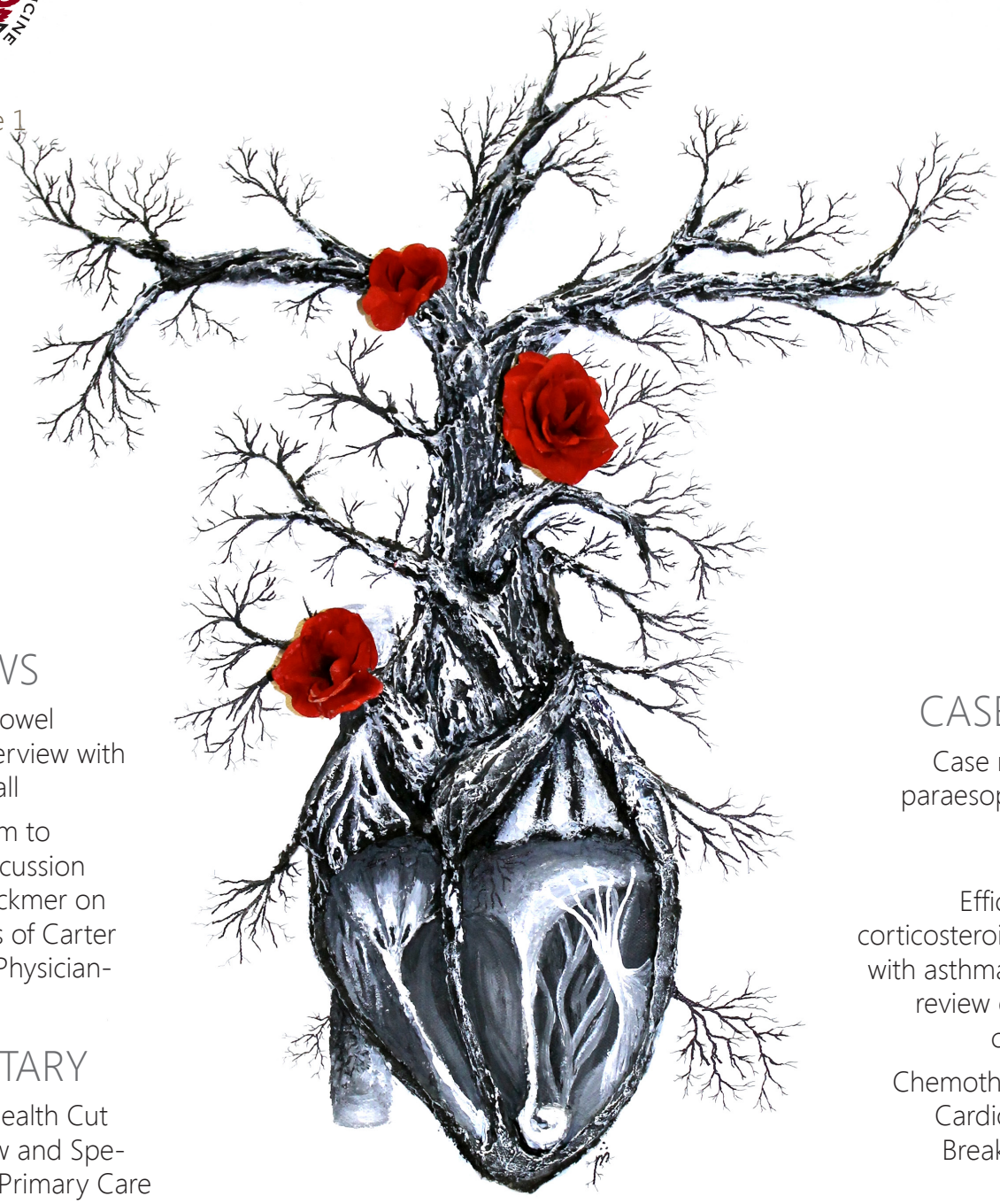

INTERVIEWS

Inflammatory Bowel Disease: An interview with Dr. John Marshall

From Courtroom to Bedside - A Discussion with Dr. Jeff Blackmer on the Implications of Carter v. Canada and Physician-Assisted Death

COMMENTARY

2015 Ontario Health Cut Backs: Overview and Specific Impact on Primary Care

CASE REPORT

Case report: Type IV paraesophageal hernia

REVIEW

Efficacy of inhaled corticosteroids for patients with asthma: a descriptive review of randomized controlled trials

Chemotherapy Induced Cardiotoxicity: Facts, Breakthroughs, and Challenges.

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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, review articles, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French, and represent the only 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 au Canada.

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TABLE OF CONTENTS

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

NEWS

CASE REPORT

REVIEWS

HUMANITIES

UOJM: Preface

University of Ottawa Journal of Medicine (UOJM) Volume 5, Issue 1 marks the fifth anniversary of publication of the UOJM after an extended hiatus. During the fourth cycle, we have taken significant strides in the functionality and scope of the journal by implementing the Online Journal System, expanding UOJM's promotion and collaboration efforts, and expanding the journal to a biannual publication. Additionally, in an effort to enhance the global reach of UOJM, we have worked to establish new international partnerships with the Shanghai Jiao Tong University, China, a partner of the University of Ottawa Faculty of Medicine at the University of Ottawa. Locally, our efforts have garnered us a booth at the 2015 Ontario Medical Students' Weekend (OMSW) at Queen's University, which can facilitate the outreach of UOJM within various academic institutions in Ontario.

The publication of UOJM would not be possible without the significant dedication and support of medical and graduate students at the University of Ottawa who have contributed not only as authors, editors, and reviewers, but also in the effort to promote and accrue sponsorship to make this issue a success. In addition, we would like to acknowledge our faculty advisors Drs. Phil Wells, Melissa Forgie, and David Moher for their guidance and direction of the journal and the editorial team training process. Finally, we would like to sincerely thank our sponsors without whom publication of the UOJM would not be possible: Faculty of Medicine (University of Ottawa), VP Research (University of Ottawa), Department of Cellular and Molecular Medicine (University of Ottawa), The Ottawa Hospital, The Children's Hospital of Eastern Ontario (CHEO), The Royal Ottawa Mental Health Centre.

Issue 5.1 represents our largest issue to date with 14 publications written by students, clinicians, and researchers. In addition to publishing articles ranging from clinical case reports, interviews, scientific reviews, and commentaries, we have included a new Humanities section within the journal to reflect the growing importance of the arts in science and medicine. Notably, this issue highlights cutting-edge research and updates in the area of "Chronic disease". Being highly prevalent in our society and imposing a significant burden on the healthcare system, as well as the quality of lives of patients, chronic illnesses are a compelling topic for researchers, clinicians, and trainees. It is imperative to better understand the mechanisms of chronic disease through research such that practice-changing breakthroughs may be possible in our future. In this issue of UOJM, we feature articles on the topics of chemotherapy-induced cardiotoxicity, physician-assisted suicide, inflammatory bowel disease, management of chronic disease in medical practice, and humanities in medical education. Printed in UOJM 5.1, you will find a case report, several commentaries, reviews, interviews, and a poem. We hope you enjoy the Chronic Disease Issue!

Ariana Noel Nischal Ranganath
Editors-in-Chief

JMUO: Préface

Le Journal médical de l'Université d'Ottawa (JMUO) Volume 5, numéro 1, marque le cinquième anniversaire de la publication du JMUO après une interruption prolongée. Au cours du quatrième cycle, nous avons fait des progrès significatifs dans la fonctionnalité et la portée de la revue par la mise en œuvre du Online Journal System (OJS), l'augmentation de la promotion et des efforts de collaboration du JMUO, et la publication biannuelle du journal. Par ailleurs, dans un effort d'améliorer la portée mondiale du JMUO, nous avons travaillé à établir de nouveaux partenariats internationaux avec l'Université Jiao Tong de Shanghai, en Chine, un partenaire de la Faculté de médecine de l'Université d'Ottawa. Localement, nos efforts nous ont valu un stand au Ontario Medical Students' Weekend (OMSW) 2015 à l'Université Queen's, ce qui facilitera la sensibilisation du JMUO au sein de diverses institutions universitaires en Ontario.

La publication du JMUO ne serait pas possible sans le dévouement et le soutien important des étudiants en médecine et de cycles supérieurs à l'Université d'Ottawa qui ont contribué non seulement comme auteurs, éditeurs et critiques, mais aussi dans l'effort de promotion et de parrainage pour faire de ce numéro un succès. De plus, nous tenons à remercier nos conseillers pédagogiques Drs. Phil Wells, Melissa Forgie, et David Moher pour leurs conseils et leur direction dans la réalisation du journal et dans le processus de formation de l'équipe éditoriale. Enfin, nous tenons à remercier sincèrement nos sponsors, sans qui la publication du JMUO ne serait pas possible: Faculté de médecine (Université d'Ottawa), Vice-président de la recherche (Université d'Ottawa), Département de médecine cellulaire et moléculaire (Université d'Ottawa), L'Hôpital d'Ottawa, Le Centre hospitalier pour enfants de l'Est de l'Ontario (CHEO), Le Centre de santé mentale – Royal Ottawa.

Le numéro 5.1 représente notre plus grand numéro à ce jour avec 14 publications écrites par des étudiants, des cliniciens et des chercheurs. En plus de publier des articles allant de rapports de cas cliniques, entrevues, revues scientifiques, et commentaires, nous avons inclus une nouvelle section « sciences humaines » au sein de la revue pour tenir compte de l'importance croissante des arts dans la science et la médecine. Notamment, ce numéro met en évidence la recherche de pointe et les mises à jour dans le domaine de la "maladie chronique". Étant très répandue dans notre société et en imposant un lourd fardeau sur le système de soins de santé, ainsi que la qualité de vie des patients, les maladies chroniques sont un sujet captivant pour les chercheurs, les cliniciens et les apprenants. Il est impératif de mieux comprendre les mécanismes de la maladie chronique grâce à la recherche pour que des progrès dans la manière dont nous pratiquons puissent être possible dans notre avenir. Dans ce numéro du JMUO, nous présentons des articles sur les thèmes de la cardiotoxicité induite par la chimiothérapie, le suicide médicalement assisté, la maladie inflammatoire de l'intestin, la gestion des maladies chroniques dans la pratique médicale, et les sciences humaines dans l'enseignement médical. Imprimé dans le JMUO 5.1, vous trouverez un rapport de cas, plusieurs commentaires, des critiques, des entrevues, et un poème. Nous espérons que vous apprécierez le numéro des maladies chroniques!

Ariana Noel Nischal Ranganath
Rédacteurs en chef

Inflammatory Bowel Disease: An Interview with Dr. John Marshall

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ABSTRACT

Dr. John Marshall is a Professor of Medicine, a Full Member of the Farncombe Family Digestive Health Research Institute, and Head of Clinical Research for the Division of Gastroenterology at McMaster University. He is also Chief of Service for Gastroenterology at Hamilton Health Sciences. Dr. Marshall's clinical and research interests include Inflammatory Bowel Disease (IBD), a group of chronic disorders that cause prolonged inflammation of the gastrointestinal tract. We were able to speak with Dr. Marshall about his clinical and research experiences with IBD and his advice for interested trainees who want to pursue a career in academic medicine.

RÉSUMÉ

Dr. John Marshall est un professeur de médecine, un membre à temps-plein du Farncombe Family Digestive Health Research Institute, et Chef de recherche clinique pour le département de gastoentérologie à l'Université McMaster. Il est aussi chef de service de gastroentérologie à Hamilton Health Sciences. Les intérêts cliniques et de recherche du Dr. Marshall incluent les maladies inflammatoires chroniques de l'intestin (MICI), un groupe de maladies chroniques causant une inflammation prolongée du tractus gastrointestinal. Nous avons eu la chance de discuter avec Dr. Marshall au sujet de ses experiences cliniques et de recherche avec les MICI, ainsi que son avis aux étudiants intéressés à poursuivre une carrière en médecine académique.

Tell us a bit about yourself, your background in health care, and your clinical and research interests.

I am an adult Gastroenterologist at McMaster University. Right now I wear a few different hats. On the university side, I am a Professor of Medicine, so I am involved in teaching, research and all things that universities do. On the hospital side, I am the Chief of Service for Gastroenterology at Hamilton Health Sciences. In terms of my background, I went to medical school at Queen's University in Kingston and actually did an undergraduate degree in Russian Studies, also at Queen's. I did just enough science to get into medical school. After medical school I came to Hamilton, which is where I have stayed since. I did my internship, residency, and my fellowship in Gastroenterology here. I then did a Master's degree in Health Research Methodology (HRM) with the Department of Clinical Epidemiology and Biostatistics. In terms of my clinical interests, I still see all forms of gastroenterology, so I haven't limited my practice, but most of what I see is Inflammatory Bowel Disease (IBD). I see more IBD than most of my colleagues here and I enjoy that. In terms of research interests, I have done many different things over the years including work in Irritable Bowel Syndrome, particularly post-infectious Irritable Bowel Syndrome, but also more recently related to IBD. I have also been involved in gastrointestinal bleeding, endoscopy and health economics, so I have seen lots of variety over the years.

How did you initially become interested and involved in Inflammatory Bowel Disease research?

I think there is lots of reasons people, including me, get interested in IBD. I think one of the pleasures of dealing with patients with IBD is that these are some of the patients in gastroenterology clinics that we get to know for many years. I finished my fellowship training in 1997, eighteen years ago, so there are people I have seen continuously for eighteen years. I get to know their lives. I get to see them go through different stages. One of the things about IBD which is challenging for patients but really, I think, rewarding for those of us who look after them, is that they tend to come to us young. We see them go through all significant stages of life, including going to school, getting married, having children, and starting careers. If they get good care and if they do well you can really see them succeed through all these stages and I think you can see the impact of good care on people's lives much more acutely. It is great to get know people through all these stages. These are young people so they will probably still be in my practice when I retire. The other reason to get inter-

Keywords: Inflammatory Bowel Disease; Gastroenterology; Crohn's Disease; Colitis

ested in Crohn's and colitis is who you are exposed to in terms of colleagues and mentors. I did a lot work as a resident with Dr. Jan Irvine who was on Faculty here at the time and also Dr. Ken Croitoru, who both have interests in IBD and I think working with them drew me to the area and inspired me to some extent. I think it is the condition itself that is interesting but also the people you meet along the way.

Tell us about your past/current Inflammatory Bowel Disease research projects.

When I did my Master's degree for the HRM program, I did a thesis project. That thesis was comparing ileoscopy with radiologic studies, small bowel meal with pneumocolon, for investigation of terminal ileal Crohn's disease [1]. We looked at the accuracy of each test for detecting disease relative to a gold standard expert consensus panel. That was a big project I did all by myself, 120 patients. It got published and obviously that was rewarding at the time. I have done lots of different studies over the years since. Early in my career I had a great interest in health economics. I did some work looking at cost-effectiveness of different therapies for IBD, specifically around biologic therapy for Crohn's disease [2]. When infliximab was first introduced, there was a lot of debate around its cost relative to its benefit and I actually did one of the big cost-effectiveness analyses for a government agency that was looking at the issue. That was hard work but also very rewarding and it is something that has still been cited many years later.

More recently, I have been doing some work looking at Nurse Practitioners. We are one of the few IBD centers in Canada to have a Nurse Practitioner with a practice focused in IBD, so we have been doing some work looking at the impact of that Nurse Practitioner on the care of patients and their health outcomes. Another thing I have been involved with is looking at the experience of some of our pediatric patients. We are one of the few centres in Canada that have both pediatric and adult IBD care under the same roof, so we have used this as an opportunity to look at the experience of some of the children with IBD transitioning to adult care. Plus, we, like many other centres, participate in multicentre trials looking at therapy for Crohn's and colitis. For those trials, we may be just one recruiting centre of many, but it is both interesting academically and good service to our patients to make sure they have access to new and emerging therapies through participation in clinical trials. Finally, we are also participating as a recruiting centre for a large project with Crohn's and Colitis Canada, the GEM project, looking for some of the early causes of Crohn's and colitis in people who are at risk because of a family history of IBD. Those are some of the projects I have been involved with and still have going on.

Can you tell us a bit about Inflammatory Bowel Disease and its current management? What is the current state of health in patients with Inflammatory Bowel Disease? How could the current state of health in these patients be improved?

When we talk about the term IBD we are referring to two different but similar conditions that we call Crohn's disease and ulcerative colitis. Ulcerative colitis is inflammation of the colon that always affects the rectum but spreads proximally to a varying degree in different people, sometimes as far as the cecum, but it only affects the colon and does not spread to other parts of the gastrointestinal tract. Crohn's disease, however, is a "gum-to-bum" disorder that can affect any segment of the gastrointestinal tract, most often the terminal ileum, the last section of the small bowel, but you can have disease anywhere in the digestive system. In Crohn's disease, the inflammation can go deeper than the wall of the gut and even burrow through it to form tunnels called fistulas that can lead to complications like abscesses. Crohn's disease is also a little more prone to scarring and fibrosis that can lead to bowel obstructions. These two conditions are very similar in that they are both inflammations of the lining of the gut but they have some differences. A lot of people would argue that Crohn's disease is probably not just one condition but many conditions that we lump together as Crohn's disease since it is very heterogeneous and each patient with Crohn's disease tends to have a very different story.

Crohn's and colitis are not just short-term problems; they are life-long conditions. There is no cure for either of these, so once people are diagnosed, they will carry that diagnosis for the rest of their lives. I think a change in our approach to IBD patients over the last ten years has been to look less just in terms of how people feel today but really looking at how well their disease is controlled over the long run, because our eye is much more on the horizon in making sure that they do well in twenty or thirty years, not just today. I think that thinking has changed our approach to Crohn's and colitis and remember, as I said before, it affects young people at a very important stage of life, so good control of disease early could have big effects on people's life experiences. I have to say I do not think I am very old yet but in my career I have seen a huge change in what people can expect from a diagnosis of Crohn's and colitis. Twenty years ago we were really treating people largely with steroids and a lot of surgery with a lot of complications from both treatment modalities. I think a lot of the problems we were dealing with back then were the complications rather than the disease itself. Now we have a lot more treatments available and I think we have a better understanding of the importance of early control of inflammation and so the expectation of someone diagnosed with Crohn's or coli-

tis in 2015 is much different from someone who was diagnosed twenty years ago. I think if we do things right almost all of these patients should expect a normal quality of life and that is a real switch in how people with Crohn's or colitis do.

When treating, one thing that we do very carefully now is try to risk stratify people. We look both at how active their disease is but also look for any signs that they could face a benign or more aggressive course of disease over their life. That said, we could treat people with similar symptoms very differently depending on whether we think they are high or low risk. In a high risk person, even if they do not feel that unwell or are not that sick, we might treat very aggressively because we know that control of their disease early can have downstream benefits and vice versa. In someone who has a very benign form of disease, we may be happy just to give short term treatment and not necessarily commit to long term therapy. So we look both at how active the disease is and how high or low risk the patient is.

For short-term treatment, sometimes we still need to use corticosteroids but we are trying to use less and less over time because we know they have short- and long-term side effects. We have a class of therapies referred to as immunomodulators or immunosuppressants such as methotrexate and azathioprine. There has been a little debate around azathioprine in the last few years around safety; we know it does have some potential side effects, including increased risks of lymphoproliferative disorders in young patients, so these days we are having very careful discussions about risks and benefits with patients that we start on these therapies. No question, the biggest change in our management has been the arrival of biologic therapies. We now have three anti-TNF monoclonal antibodies available for treatment of Crohn's or colitis and those are adalimumab, infliximab, and golimumab. Just recently approved in Canada is another biologic called vedolizumab, which has a different mechanism of action by interacting with leukocyte trafficking. We have a lot more options than we used to, and these drugs have really been the ones that have changed the outlook and expectations for people with Crohn's or colitis. They are expensive but they are also very effective both in the short and long run. When we get back to thinking about the costs and the benefits we can make a strong argument that the benefits really do outweigh the costs with biologics. Surgery is sometimes necessary, but I think the proportion of patients going into surgery these days is much lower than what it was twenty years ago, and I think that's because we have better medical therapy. However, there are situations where surgery is still the best option, but again, it is less common than it used to be.

What research work do you think is needed in Inflammatory Bowel Disease? What direction would you like to see Canada take with regards to management of this chronic disease?

I think there is lots of research still to be done in Crohn's and colitis, and I think we are in a very exciting era where we have new technologies that may give us new answers about understanding what causes Crohn's and colitis and obviously how to treat it better. One thing we really need more information about is our predictive tools. We need better ways of risk stratifying patients and dividing people into high and low-risk phenotypes so we can invest our most expensive and effective therapies in the people who would really stand to benefit the most. The predictors we have right now are a little blunt. They are not that accurate, so we need better tools to do that. There is also a lot of work being done looking at genetics, serologic markers, and aspects of the gut microbiome, as well as predictors of response to therapy. There is lots of animal work showing that the microbes in the gut are part of the inflammation that drives Crohn's and colitis, but we are just beginning to understand whether we could modify the microbiome in a way to help control the disease, and I think that is a frontier which will be the topic of a lot of discussion and activity in the next couple of decades as technology is getting better to try to profile the microbiome. Medical informatics is a huge field that needs more manpower because it's a new area of specialty as we are getting more, better tools and methodology to crunch all the data that are produced from analyzing the microbiome, the virome of the stool, and the proteome of the blood as well. There is all sorts of technology that is just emerging that hopefully will give us some of these answers.

What advice would you give to students who want to pursue this kind of career? Can you describe what your weekly schedule is like? How do you balance your family and work life?

I think one of the reasons I went into gastroenterology is because I never met an unhappy gastroenterologist who regretted their career decision and I still have yet to meet one. Gastroenterology is a great field of clinical activity partly because we deal with a whole range of people in age and acuity of illness. We deal with very sick people, for example with bad IBD, and we also deal with perfectly healthy people having screening procedures for cancer detection. We deal with both younger and older people so there is a lot of variety there, plus our weeks are varied. We have days when we are seeing patients in the clinic, days when we are doing procedures in the endoscopy suite, and days when we are managing patients in the hospital. There is a lot of variety in gastroenterology that keeps people very engaged and seems to sustain people's enjoyment of their career over time. There

is no question it is hard work if people want to do both clinical gastroenterology and pursue an academic career in teaching and research; it is a lot of balls that you need to keep in the air, but, like anything in life, if you really enjoy what you are doing and find it rewarding, then the hard work doesn't seem as onerous and there are lots of rewards in terms of job satisfaction. I think anyone starting a career in medicine needs to find what they really enjoy and follow that. You cannot be too focused on the short-term goals such as getting the right job this year; you have to really look at the long-run. If you enjoy what you do and if you work hard at it the opportunities will present themselves. It is a bit of a challenging time in Canada right now for careers in gastroenterology. The number of people being trained has increased so there has been more competition for jobs, but my observation is that good people always find the right job eventually and there needs to be a bit of patience.

It will always be a challenge in a busy career and in any branch of medicine, trying to balance personal life versus professional life. Professional life in medicine can be all-consuming and I think you just need to find ways to block off time for yourself. In an academic career, there are times when you can do some of your work from home or after hours so you could move some of it around to create flexibility. I think even though my work has been pretty busy, I have still found ways to spend occasional days with my kids and I still made their Christmas concerts and watched their sports games, so it can be done. I think you have to recognize that you do not have to say yes to every opportunity that comes your way. That is very difficult when you are starting out in your career because medicine is full of exciting opportunities and places to go, meetings to attend, patients to see and the hardest word anyone ever learns in medicine is to say "no." Sometimes you have to say no and the same opportunities will present themselves down the road, but don't be dissuaded, it's a great career.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. John Marshall for graciously taking the time to answer all of our questions and for approving the final version of this article. For further information about Dr. Marshall and his research projects, please visit his research group's website at http://farncombe.mcmaster.ca.

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From Courtroom to Bedside - A Discussion with Dr. Jeff Blackmer on the Implications of Carter v. Canada and Physician-Assisted Death

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INTRODUCTION

On February 6th, 2015, the Supreme Court of Canada (SCC) concluded that "s. 241 (b) and s. 14 of the Criminal Code are void insofar as they prohibit physician-assisted death for a competent adult person who (1) clearly consents to the termination of life; and (2) has a grievous and irremediable medical condition (including an illness, disease or disability) that causes enduring suffering that is intolerable to the individual in the circumstances of his or her condition." [1]. The Court added: "We would suspend the declaration of invalidity for 12 months" [1], to allow the government to respond with appropriate legislation to guide and regulate the practice of Physician-Assisted Death (PAD).

The Canadian Medical Association (CMA) will play a leading role in helping the Government of Canada craft this new legislation. We met with Dr. Jeff Blackmer, the Vice President of Medical Professionalism at the CMA. He holds a Master's in Medical Ethics from the University of Toronto. He also served as the Executive Director of the CMA's Office of Ethics, Professionalism and International Affairs and has been the interim Director of Ethics for the World Medical Association in Geneva. In an interview on February 11th 2015, Dr. Blackmer kindly agreed to help us navigate through an array of ethical and practical ramifications stemming from the decision in Carter v. Canada. In this interview, Dr. Blackmer addresses the ethical grounds on which the decision stands, who will potentially qualify for PAD, as well as issues moving forward as a medical profession and legislatively as a nation.

PART 1: RAMIFICATIONS

The SCC's decision does not require one to be terminally ill to seek Physician-Assisted Death. How does this affect future legislation on who can access such a service?

We need to determine whether that closes that conversation constitutionally or if there is still scope for further input. My feeling is that there would be much more support for a tighter framework in terms of requiring that the patient be terminal. This is not to minimize in any way the suffering of people who do not have a terminal illness, it is just that for a lot of doctors, this opens too many doors and generates too many questions. If you look at most of the US states, the laws are very tight [regarding terminal patients]. There has not been any evidence of abuse or slippery slopes, because they are so clear. My conversations with doctors to date indicate more of a comfort level with tight parameters. The Netherlands has broader inclusion parameters and Belgium and Switzerland even more so. Our initial read [of the decision] is that we might have very little ability to influence [how those parameters will be developed in Canada].

The Supreme Court also defines a grievous and irremediable medical condition as including "an illness, disease or disability" [1]. How do we define what is admissible and what is not, for example blindness?

Because grievous […] is not a technical medical term, what is grievous to one person may not be to another. I think what they intended by "irremediable" was that it is something that cannot be cured. For example blindness would fall into that category. This is where I think we need to be careful. Some people will say those are the type of patients who should qualify and this was the intent. Others say, that is not what this should look like. We will be reaching out to the [CMA] membership, to take the pulse on some of these issues.

The Supreme Court's conclusion allows for "competent adults". Do we deprive children of this service? If not, how do we regulate and safeguard that practice?

We have seen from the experience in Belgium and Holland that things have changed over time to include protocols for children and for newborns. In Holland, I do not think it is written into the legislation, but it is allowed implicitly and they have developed protocols [concerning euthanasia in newborns] called The Groningen Protocol [2]. There is definitely a feeling, and maybe for some people a fear that if there was a constitutional challenge based on age discrimination, PAD may have to be also made

Keywords: Physician-Assisted Death; Physician-Assisted Suicide; Supreme Court of Canada; Euthanasia; Medical Ethics

available to children. The term adult will need to be defined, because that varies by province, and I think this should also be federally legislated.

Would chronic depression be admissible as a "grievous and irremediable medical condition that causes enduring suffering intolerable to the individual" [1]?

My reading of it is that yes [chronic depression] probably [would be admissible for PAD]. For example, I look after spinal cord injured patients. For those folks, I think there are a lot of conditions where they would be able to say: I have this irremediable illness, my spinal cord is never going to be cured, I'm in intractable pain and suffering, and I want to access PAD. On a reading of the Court's judgment, I think that they would qualify for [PAD], which causes some concern amongst medical practitioners. There have been very controversial cases in Europe. There was an elderly woman from Britain who said that she could not keep up with the pace of technology and change, she just did not want to live anymore as it was all too much for her. She was assisted in dying. There are many examples that are [of concern], that [could potentially] qualify based on what the Supreme Court has said.

PART 2: ETHICS

What are some of the ethical principles that guided this ruling and make this a positive outcome and some ethical areas in which this ruling may fall short?

From an ethical and moral standpoint, some CMA members are saying: This is not why I went into medicine. I went into medicine to cure when possible, care always, but not to hasten the dying process. Many CMA members say that PAD muddies those waters; it changes the foundational nature of the doctor-patient relationship. We will need to set parameters to be as clear as we can be, on how that process is going to work, so that when the doctor enters the room, one does not wonder why they are there. From the positive perspective, some members have told us, they feel it is their ethical responsibility to do everything they can to alleviate pain and suffering, up to and including assisted dying. The patient autonomy/self-determination piece is also a big ethical reason why a number of doctors say they want to participate. They want to be able to respect their patients' final wishes.

You previously mentioned that "The Supreme Court has established this as a right and now it is a matter of defining the parameters of who qualifies". If PAD is a right, is it not a right for everyone?

Not necessarily, and that argument was put forward at the SCC. Some civil libertarians say: one need not be sick, one just needs to want access. As a society, we can still define those parameters. We can have a justifiable infringement of Charter rights based on other circumstances, and that is basically what the ruling was in Rodriguez. They said it is an infringement on your [section] 7 Charter rights, but it is a justifiable infringement, based on other societal considerations and concerns, and our obligation to protect the vulnerable.

How do we reconcile this new direction in healthcare with the Hippocratic Oath and other founding principles that have guided medicine thus far, like "first do no harm"?

There are members on both sides of this. Some say: I'm doing harm by allowing my patient to suffer. So, being able to assist them in the dying process is helping me to alleviate that harm, pain and suffering. Others view assisting in dying as harm unto itself. If you look back on the original Hippocratic Oath, it said you could not participate in abortion, yet abortion is legalized. Our approach to abortion has changed. Now, because of this ruling, our approach to assisted dying is also evolving. We need to keep that in mind when trying to interpret these things literally. At the same time, we must respect doctors who say: "No, I do take that literally, I do not want to do these things, that is not part of my job and that is not why I am here". We respect [those views] and also respect the views of doctors who are comfortable participating in those activities, which are legal.

How will this new practice of PAD resemble and differ from the current end-of-life practices of escalating palliative sedation and withholding or withdrawing lifesaving or life-sustaining medical treatment [3]?

[One] can argue both sides, but [the difference between PAD and] terminal sedation [and] the escalation of doses, is all a question of intent. There is a fine line because it is very subjective. Some people consider this as a natural extension of aggressive pain and symptom management and there is something to be said for that. The Palliative Care Doctors Association has been very clear and very consistent that this is not something they intend to embrace, so it may be a situation where we need clarity between where palliative care ends and where assisted dying begins.

PART 3: MOVING FORWARD

What will be the CMA's role moving forward in crafting the new legislation?

The CMA is coming up with a draft framework that will be reviewed and discussed by the CMA's Committee on Ethics and Board of Directors, followed by a two-month consultation period with members. Then, at the General Council meeting in August, we will present what the CMA thinks legislation should look like. Many doctors do not like the decision and that is OK, but

ultimately it is society, through its elected representatives and courts that is making these rules and decisions. Basically, the profession is saying OK, whether you agree with this or not, the SCC has ruled, so the time for that discussion has passed and now we need to make sure that we help the government get it right.

Who will decide who is admissible for this service? Will it be two physicians or a multidisciplinary panel, etc.?

The CMA's consultation process will [address] that. My [sense], is that it is going to require more than one physician. [There has been] talk about judicial panels, and I think that is probably a little bit far reaching, based on the SCC's decision and what would be practical and feasible. I think we are going to try to keep this as a medical rather than judicial decision. There are also some advantages to trying to involve physicians who really know the patient because these situations are very complex.

How do we protect the rights of medical professionals who choose to offer these services and those who choose not to?

The broad strokes are pretty clear; doctors who want to participate, can, and the CMA will support them. We are looking at what that support looks like. For example, in Holland, the Royal Dutch Medical Society has a whole unit that helps members who want to participate in assisted dying. For those who do not want to participate, the basic principle is this: If you do not want to, you do not have to do it and no one is going to force you to do it. I have not heard anyone say anything to the contrary. The real crux of the issue is what I call the referral question. If I refuse to participate, do I then have a moral, legal, or regulatory obligation to refer to someone who will provide that service? The Ontario and Saskatchewan Colleges of Physicians have draft guidelines, not finalized nor approved yet, but draft policy that would require physicians to make a referral. These do not specifically address euthanasia or abortion, but rather the whole issue of conscientious objection. Understandably, a number of our members are very concerned. Now the flip side of that is the issue of access. To what extent can physicians exercise their moral views if this has a detrimental impact on patient care? CMA policy is essentially silent on mandatory referral. As a result of [the CMA] being silent, the policy has been interpreted as saying [referral] should not be mandated, which is probably accurate. We need to have a more open discussion on this as part of discussions on the legislated framework.

The Court refers to the "limits of palliative care in addressing suffering" [1]. What can we do to improve palliative care across Canada and ensure that this new legislation strengthens it and does not diminish it?

This is a critical point. Only about a third of Canadians have access to good quality palliative care. What we have seen in other countries is that palliative care services actually seem to have improved in some of the jurisdictions where assisted dying has been legalized. With the dialogue about dying being out in the open, there tends to be an increased focus on palliative care as well. The CMA is in the process of preparing a report to be released in May at the Palliative Care Doctors annual meeting looking at the current state of palliative care in Canada with recommendations to improve access to palliative care.

How can medical students, residents, physicians get involved in helping to craft this upcoming legislation?

The CMA will be reaching out to members, other organizations and stakeholders in the summer to get their views. We welcome medical student and resident participation. If people want to get in touch with me at Jeff.Blackmer@cma.ca, I will make sure they are included in those communications. All Canadians can participate by writing to their MP.

CONCLUSION

In the wake of this historic decision by the Supreme Court of Canada, Canadian physicians will shoulder the responsibility of helping the Government craft legislation to ensure the practice of Physician-Assisted Dying is safe and fair. As Dr. Blackmer said: "whether you agree with this or not, the SCC has ruled, so the time for that discussion has passed and now we need to make sure that we help the government get it right". As this interview has illustrated, there are many facets and challenges to implementing PAD. With early indication that physician and public comfort levels are trending toward a more restrictive approach to who qualifies for PAD, it will be interesting to see how the legislation develops around the SCC's broad inclusion criteria.

ACKNOWLEDGEMENTS

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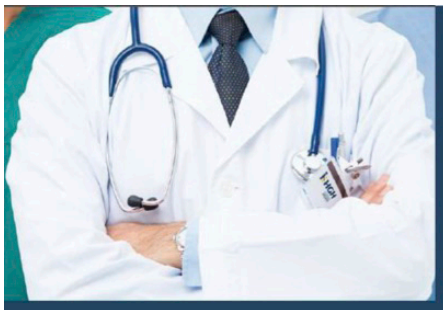

Improving Chronic Kidney Disease Management Using Wagner's Model for Chronic Care

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ABSTRACT

With an aging population, chronic disease will place an increasing burden on the health care system. Consequently, the Canadian health care system needs to implement systemic changes to manage chronic disease effectively. This paper applies the six basic elements for improving chronic care found in Wagner's Chronic Care Model (CCM) to the management of chronic kidney disease. A fictional patient, Paul, is used to demonstrate the usefulness of this model in managing chronic diseases at a systemic and individual level.

RÉSUMÉ

Avec une population vieillissante, les maladies chroniques imposeront un fardeau de plus en plus lourd sur le système de soins de santé canadien. Par conséquent, il faudra mettre en œuvre des changements systémiques pour gérer efficacement les maladies chroniques. Cet article applique les six piliers de base pour l'amélioration des soins chroniques, trouvés dans le modèle des soins chroniques de Wagner, à la gestion de la maladie rénale chronique. Un patient fictif, Paul, est utilisé pour démontrer l'utilité de ce modèle dans la gestion des maladies chroniques à un niveau systémique et individuel.

INTRODUCTION

Paul is a 45-year-old patient in your family medicine practice who you recently diagnosed with polycystic kidney disease (PKD), a genetic condition that leads to kidney cyst formation. There is no cure for PKD, and Paul's two teenage daughters are also at risk. As a result, Paul will need long-term care for chronic kidney disease. Chronic kidney disease (CKD) is characterized by a progressive and irreversible insult to kidney function. Fluids, electrolytes, and wastes build up as kidney function declines, causing symptoms such as fatigue, nausea, and confusion [reference]. Although there is no cure for CKD, there are strategies to delay the need for renal replacement therapy (RRT), which includes dialysis or transplantation [1]. Management of CKD is multifaceted, involving medications, diet, lifestyle changes, and patient education, with the ultimate goal of slowing the progression of CKD and improving quality of life [1,2].

With the aging Canadian population, the increasing incidence of chronic disease puts a strain on health care delivery [3]. Diabetes and hypertension, the two most common etiologies of CKD, are becoming more common with the aging population [1]. If CKD is not properly managed, it can lead to many complications, such as cardiovascular disease, malnutrition, hormonal imbalance, and bone disease. These complications can decrease a patient's quality of life, lead to dialysis or kidney transplant, and increase long-term health care spending [1]. The increasing incidence of CKD requires effective management solutions to prevent an overwhelming public health burden. For example, multidisciplinary teams are critical in the management of chronic disease, and, in regards to CKD, they may slow the rate of decline in renal function [2]. In one study, CKD care programs reduced the probability of emergency dialysis and hospitalization and lowered medical costs [2]. One similar care program that practicing physicians can implement is Wagner's Chronic Care Model.

Wagner's Chronic Care Model (CCM) outlines six basic elements for improving chronic care [4]. First, the CCM requires a delivery system with well-defined team members, planned visits, regular follow-up, and case management. Next, the organization of healthcare involves supporting improvement strategies, systematic handling of problems, incentives based on quality of care, and care coordination agreements. Embedding evidence-based guidelines into clinical practice, integrating specialists and primary care, and sharing information with patients are crucial for decision support. Next, clinical information systems should provide reminders, share information with providers and patients, facilitate care planning, and monitor performance. Encouraging

Keywords: CKD; Chronic Kidney Disease; CCM; Chronic Care Model; Wagner

patient participation in programs, forming partnerships with community organizations, and advocating for policies to improve care addresses community resources and policies. Lastly, the healthcare system needs to emphasize patients' central role in their own care by using self-management support strategies and resources [3-5]. Both an informed and active patient and a prepared and proactive team must embrace these elements to ensure productive interactions and shared care planning [4,5]. The components of the CCM are demonstrated in Figure 1. Through Paul's mock case scenario, this paper will demonstrate how each element of the CCM contributes to an effective model in managing chronic kidney disease.

HEALTH SYSTEMS

Delivery System Design

After a diagnosis of CKD, patients are more likely to return to their family physician for initial follow-up than see a nephrologist [6]. Additionally, as part of the multidisciplinary team, family physicians are encouraged to actively manage CKD prior to referral to nephrology, as it improves patient outcomes by avoiding missed opportunities for early treatment [6]. As the family doctor in the mock scenario, you begin Paul on a course of ACE inhibitors to lower his blood pressure and begin monitoring his kidney function. However, research demonstrates that family physicians do not have enough time to deliver the recommended services for chronic disease management [7]. These clinics utilize a multidisciplinary team to provide the full spectrum of CKD care, including patient education and self-management, in accordance with the CCM [8].

Two months after his diagnosis, Paul visits the CKD clinic and is introduced to the team. Paul's case manager is a trained Nurse Practitioner who will meet with him regularly to decide which areas of the clinic he would need to access. Paul's team also includes a dietician, a pharmacist to review medications and monitor blood work, a social worker to help address medical expenses, a counsellor, and a nurse to help Paul set lifestyle goals. A nephrologist will meet with Paul on regularly scheduled intervals to manage his kidney disease. Finally, office assistants will manage administrative capacities and ensure operations run smoothly. Paul leaves his first meeting overwhelmed with information, but motivated to be an active team member. All the clinic's instructions and roles are given to Paul in a prepared information package for him and his family to review at their leisure. When Paul returns to the CKD clinic for a second appointment, the team creates a long-term care plan with Paul and forwards it to you, his family physician. At scheduled follow-up visits, Paul meets with various members of the team based on his needs. As Paul begins his journey at the CKD clinic, you continue to monitor his health, while closely following his daughters for any sign of PKD. Paul's daughters may be referred to a medical geneticist if they are interested in screening for PKD at a later date.

Organization of Healthcare

To manage Paul, healthcare organization involves monetary government support; evidence-based CKD guidelines; and formal self-improvement programs for the family physician, nephrologist, and CKD clinic. These efforts work to support improvement strategies and handle any problems strategically. One member of the CKD team would address quality improvement and patient safety, involving issues like prescription management, secure medical records, and incident reporting [9]. With different team members each providing their own services, it is essential to ensure effective communication and hand-off of care. Ineffective communication is often a contributing factor in medical errors and patient harm [10]. To address this problem, service agreements between the CKD clinic and family physician would explicitly state each professional's responsibilities in the different aspects of Paul's care. The CKD clinic also incorporates incentives to encourage excellent care. For example, after meeting with his dietician, Paul is particularly impressed with his ability to take into consideration the foods he normally eats. On his way out, he nominates his dietician for "Healthcare Provider of the Month"—an initiative started by the CKD clinic to encourage all team members to provide excellent quality care.

Decision Support

In Paul's case, decision support would involve embedding evidence-based CKD guidelines into his management, integrating his specialists and primary care, and proving a platform for his doctors to share important information with him. For example, between follow-up visits, Paul comes to your family practice with a urinary tract infection (UTI). You would not normally treat asymptomatic UTIs; however, PKD puts Paul at risk for recurrent UTIs and you are unsure about prescribing antibiotics. Based on the service agreement between you and Paul's nephrologist, you send him an email inquiring about the situation. Within hours, you receive a reply from the nephrologist, who, being fully aware of Paul's medical history, accurately advises you to prescribe antibiotics and provides you with evidence-based research on the subject. You phone Paul to inform him that he should take antibiotics and electronically send a prescription to his local pharmacy.

Clinical Information Systems

The CKD clinic utilizes a unique clinical information system similar to the National Health Services' Renal PatientView [11]. This information system is accessible by Paul, the CKD clinic, and his family physician. It includes basic details about Paul's diagnosis, treatment, and test results. Paul can login to the system, enter his weight and blood pressure regularly, and monitor his health performance. He can create lists of topics to discuss with his team and automatically receives email reminders about upcoming appointments. This system is effective in facilitating individual patient care planning. For example, at an appointment with

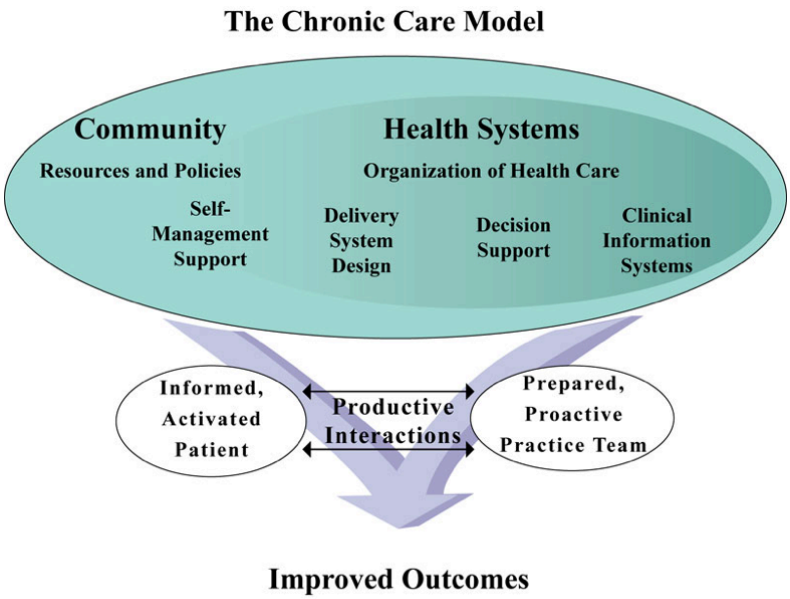

Figure 1. illustrates the different components of Wagner's Chronic Care Model and how they are used to facilitate productive interactions between the patient and healthcare team to improve outcomes.

The chronic care model [Internet]. Seattle: Improving Chronic Illness Care; c2006-2014 [cited 2014 May 11]. Available from: http://www.improvingchroniccare.org/index.php?p=The_Chronic_Care_Model&s=2

his dietician, Paul wonders if he can eat more protein. On the system, they examine Paul's blood work and health status over the past year. Paul is clinically stable and has been compliant to diets in the past. After a brief conference with the nephrologist, the dietician is able to loosen Paul's protein restrictions and monitor for any changes in his health status online.

COMMUNITY

Resources and Policies

Paul has been struggling with his diagnosis and feels guilty that his children are at risk for PKD. Paul's counsellor believes that he would benefit from an online community support group for patients with PKD and gives him information to set up an account. Using this online forum, Paul slowly comes to terms with his diagnosis and he is able to better discuss his mental health concerns with his counsellor. Using the online community, Paul works with his counsellor to advocate for better mental health awareness in his community and begins a support group for dealing with genetic disease.

At another visit, Paul mentions that he would like to add swimming to his exercise routine but cannot afford a full gym membership. His social worker is aware of the many community resources available and arranges a low-cost aquatic pass at the community centre.

Self-Management Support

As CKD does not typically display symptoms until an advanced stage, involving patients in their own management can be a challenge [8]. Early interdisciplinary team involvement fosters self-management and Paul is reminded of his important role on the team at every appointment. At each yearly assessment, Paul receives a report card on the current state of his overall health, which he uses as motivation to remain an active and informed patient.

As Paul's kidney function worsens, he will eventually require renal replacement therapy (RRT). Since only 20% of CKD patients qualify for transplant [1], the clinic has an extensive pre-dialysis education program, including talks from dialysis patients, group discussion sessions, and visits to dialysis units. This program is designed to reduce the probability of emergency dialysis and hospitalization to lower medical costs [2], and it helps Paul remain an active member when making decisions about his future care.

CONCLUSION

The Chronic Care Model (CCM) provides an effective model to manage CKD and can be applied to other chronic medical conditions. Utilizing all six elements of the CCM allows for productive interactions between Paul and his care team, as illustrated in Figure 1. Through self-management support and multidisciplinary care, Paul is given the information to confidently and effectively make decisions about his health [5]. By designing an organized health system with an effective clinical information system and decision support, Paul's health care providers always have access to his information and knowledge about the best evidence for care [5]. Combining the informed, active patient with the prepared practice team allows for Paul to set goals with his team members and improve his clinical outcomes.

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2015 Ontario Health Cut Backs: Overview and Specific Impact on Primary Care

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ABSTRACT

On February 1, 2015, the Ontario government began implementing a series of unilateral cut-backs to health care in Ontario. These changes include a 2.65% decrease to physician fees across-the-board, restricting entry into Family Health Organizations (FHO) and Family Health Networks (FHN), discontinuing enrolment premiums, and restricting the Income Stabilization program. Without a doubt, family physicians are amongst the most heavily impacted physicians. In this commentary, we attempt to summarize the recent events leading to these cut-backs, and discuss the potential implications of these changes in relation to primary care in particular.

RÉSUMÉ

Le 1er février 2015, le gouvernement de l'Ontario a commencé à implémenter une série de coupures unilatérales aux soins de santé en Ontario. Ces changements comprennent une diminution de 2,65% à l'honoraire des médecins, une restriction à l'entrée dans des Organismes de santé familiale (OSF) et des Réseaux de santé familiale (RSF), un arrêt des primes d'inscription, et une restriction du Programme de stabilisation du revenu. Sans aucun doute, les médecins de famille sont parmi les médecins les plus fortement touchés. Dans ce commentaire, nous essayons de résumer les événements récents qui ont conduit à ces coupures, et discutons des implications potentielles de ces changements par rapport aux soins primaires en particulier.

BACKGROUND

The Physician Services Agreement (PSA) is a contract that is negotiated every few years between the Ontario government and the Ontario Medical Association (OMA), the latter which represents the interests of the approximately 28,000 practicing physicians in Ontario [9]. The PSA is essentially a contract between employer and employee. It details not only how much physicians can bill for various services, but also health care financing on a greater scale, such as where health care funding should be invested, and where we can afford to cut back on certain programs and services. In recent years, the agreement has reflected a careful balance between the government's responsibility to operate within budget, and physicians' need for enough financing to serve an aging patient population.

The PSA ratified in 2012 reduced health care expenditures by making changes such as reducing annual health exams, reducing cervical cancer screenings and colonoscopies in accordance with new evidence-based cancer care guidelines, and implementing a 0.5% decrease to physician salaries [10].

Keywords: Family Practice; Family Medicine; Primary Care; Government; Ministry of Health

At the time, this contract was supported unanimously by the OMA board and by 81% of physicians in a referendum of Ontario physicians [11]. This PSA expired in March 2014, and for the past year the OMA and the Ontario government have been in negotiations for a new PSA [12].

NEGOTIATION CONFLICTS

The negotiations for the new PSA have been fraught with conflict, partly due to the government's goal of eliminating the province's deficit by 2017-2018 [13]. Ontario's deficit in recent years began with the global economic recession of 2008, which resulted in a provincial deficit of $6.4 billion in the 2008-2009 fiscal year, after three consecutive years of balanced budgets [14]. The subsequent years produced provincial deficits of $19.3 billion in 2009-2010 [15], $14.0 billion in 2010-2011 [16], $13 billion in 2011-2012 [17], $9.2 billion in 2012-2013 [18], and $10.5 billion in 2013-2014 [19]. With the projected deficit for the 2014-2015 fiscal year being $12.5 billion, the new government has inherited a large deficit that must, understandably, be eliminated [13]. Part of reducing this deficit is to reduce government spending, of which healthcare is a major portion.

Following months of negotiations, the government's final offer to the OMA was a 1.25% increase in budget for physician services. The OMA rejected this offer, citing that this increase would not be enough to cover the increasing healthcare needs of the aging population [12, 20]. Dr. Ved Tandan, president of the OMA, highlighted the fact that "Ontario's population is already underserviced for health care and our population is growing and aging. That increases the need for health services, but the government has decided to fund less than half of the additional care that will be required" [21].

This argument was refuted by Health Minister Eric Hoskins, himself a family physician, who insisted that physicians would be able to provide the same level of care as before despite the small budget increase proposed. "The OMA wants you to believe that doctors in this province can't provide the same level of care as last year unless they receive a pay raise and we simply don't agree…. doctors can't just bill more and more and more. At some point they'll have to accept that they can do roughly the same amount of work as last year for roughly the same pay" [21]. Dr. Hoskins further stated that Ontario physicians on average make $360,000 in gross income, suggesting physicians should not complain on reductions to an already-handsome salary [21].

2015 HEALTH CARE CUTS

With both sides unable to come to an agreement after nearly a year of discussion, the government left the negotiations table and announced in January 2015 that it would unilaterally impose a series of health care cuts. The earliest cuts began on February 1st, 2015 with certain changes to become effective at later dates [1, 20, 22].

The new changes are enumerated below [1-7]. Numbers 1-11 impact family physicians directly.

1. 2.65% decrease to all physician payments
This is applied to all physicians across the board. It is effective February 1, 2015 for all fee-for-service payments, and May 1, 2015 for other models of payment.

2. Reconciliation
The ministry will impose a hard cap on spending on physician service. If physicians, as a whole, bill more than this amount, money will be taken back from physicians in 2-3 years' time. It has not been specified as to how these so-called clawbacks would occur.

3. Discontinue CME program
Physicians will no longer be compensated for Continuing Medical Education (CME) activities.

4. Managed entry into Family Health Networks, Organizations and Teams
Previously, 40 new family physicians per month were allowed to join or start a Family Health Network (FHN) or Family Health Organization (FHO). This occurred under two streams - 20 in a priority stream and 20 in a stream that was first-come-first served (based on date of application).

As of June 1, 2015, only 20 physicians per month will be allowed to join FHO or FHN, and only in areas of high need (priority stream only). By default, new family physicians who do not fulfill these criteria will only be allowed to join a Family Health Group (FHG), start a solo practice under the Comprehensive Care Model (CCM), or bill fee-for-service. The only way for physicians to practice under a FHO or FHN outside of the above parameters is to act as a locum for an existing group, or replace a departing physician (ex. retiring physician) [23].

Only practices that are under the FHO or FHN model can apply to become a Family Health Team (FHT). Essentially, the only way for a physician to join a FHT is to join the FHO or FHN that has been designated as a FHT. Therefore, by limiting entry into FHO and FHN practices, entry into FHT practices will be limited as well [24].

FHOs, FHNs and FHTs are considered to provide more comprehensive care than FHGs and CCM because they incorporate a team of allied health professionals. Furthermore, they offer after-hours telehealth advisory services every day of the week. There is evidence that FHOs, FHNs and FHTs are linked to higher patient satisfaction, more patient-centered care, and better learning environments for medical students (this has been one of the reasons more students are choosing family medicine as a career).

5. Discontinue enrolment premiums
These are one-time premiums paid to family physicians for accepting new patients [25]. Exception: There are three enrolment codes that will be continued, and those are for enrolling a patient previously without a family doctor (Q023), a Fecal Occult Blood Test positive patient (Q043), and complex or vulnerable patients from Health Care Connect (Q053).

6. Discontinue Health Care Connect program
This program helps unattached patients find a family physician. The program is currently still in effect; details on its discontinuation are pending.

7. Restrict Income Stabilization program
The Income Stabilization program helps new physicians entering FHN and FHO groups by ensuring stable monthly payments in

their first year of practice, thus acting as a source of financial stability [25]. This program provided around $200 000 - $220 000/year to new family physicians [23].

8. Acuity Modifier - delay
The acuity modifier is a $40 million/year payment given to physicians who practice under models in which patient enrolment is based on the acuity of patients. Payment for these services will not be delayed for two years.

9. Reduced fee for weekend or holiday assessment of urgent medical problem (A888)
The A888 fee is reduced to from $35.40 to $33.70. This change applies to many family physicians, since this is often what is billed at walk-in clinics [23].

10. HOCC one time (per diem) payment discontinued
The Hospital On-Call Coverage (HOCC) program pays physicians who work on-call at hospitals [26]. The HOCC One Time Payment will be discontinued for HOCC groups < 5 physicians - this is a stipend for working above their minimum call shift requirements.

11. HOCC freeze
Funding for the HOCC program will be frozen. No new HOCC groups/group members will be approved.

12. Chronic Disease Assessment Premiums (E078)
This premium is given for certain physicians who accept complex patients with certain chronic conditions [27]. It will be discontinued for internal medicine, cardiology,
gastroenterology, and nephrology.

POTENTIAL IMPLICATIONS TO PRIMARY CARE

Family physicians are directly impacted in many ways by the recent health care changes. Specifically, new family medicine graduates who are looking to start or join practices are heavily affected.

The restrictions to joining FHO, FHN, and, thus, FHT practices likely arose from the fact that these newer models are more costly than traditional models based on fee-for-service such as CCM and FHG. On average, a FHO costs the government $70 000/year more than a CCM, and $30 000/year more than a FHG [23]. (See Table 1 for differences between these family practice models). The popular FHO, FHN, and FHT models have been touted as the modern way to deliver primary care. Unlike the traditional fee-for-service models, physician income under these models does not rely heavily on the number of appointments in a day [25]. Physicians therefore feel less pressure to speed through appointments. Most recent family medicine residents have been trained under these new models, but for the most part will not be able to join these types of practices once they graduate [28-32]. Even if new family physicians commit to moving to "high need" areas in hopes of joining a FHO, FHN or FHT, they can only do so if the local quota for entry into these models has not been reached. The province-wide limit for joining these models is now only 20/year [23].

The discontinuation of enrolment premiums will affect new graduates as well. It is estimated that new graduates will lose $30 000/year, and that established physicians will lose $5000/year based on this cut alone. This cut affects all new graduates, even those that decide to relocate to high need areas. The discontinuation of the Income Stabilization program, except for in "underserviced areas", will also decrease starting salaries of new graduates. All in all, new family physicians stand to lose $30 000 - $100 000 compared to the starting salaries of their predecessors [23].

Established family physicians are affected as well. There will be a 2.65% across-the-board cut to all physician services. Recently the public has been told that Ontario physicians make around $360 000 a year. However, this is not the case for most family physicians. The average gross income for family physicians is in the range of $200 000 to $ 300 000 [34]. This gross income is used to pay the overhead costs of their clinic, which include rent, equipment costs, and staff salaries. These overhead costs consume roughly 30-40% of the gross income, resulting in an average net income of approximately $175, 000 [34, 35]. Reducing the gross income of family physicians not only affects their net income, but also may reduce available funding for their clinic and thus, the quality of patient care [29, 30, 33 -38].

Furthermore, while the government insists it won't limit how many patients physicians see, there will be a hard cap on the total amount the government will spend on physicians services. If physician billings exceed this hard cap, they must pay back the excess at a later date. Unfortunately, physician billing is often dependent on patient need for health services [30, 31]. Taking back money from physicians who work above and beyond the average in order to provide for their communities may, at best, be discouraging and, at worst, penalizing to these individuals.

Currently, 900,000 Ontarians do not have a family doctor, and there are an estimated 140,000 new Ontarians, both newborns and immigrants, expected over the next year [12]. Unfortunately, there is a feeling amongst new family medicine residents that Ontario is no longer an optimal region to practice. Many new Ontario family physicians may establish themselves elsewhere - perhaps out of province, or in the United States.

Table 1. [Family Health Models in Ontario]. Description of the differences between types of Family Medicine Practice Models in Ontario

	Comprehensive model aka Fee for Service	Family Health Team	Family Health Group	Family Health Networks	Family Health Organization
Who it is for	Designed for solo family physicians	Work ininterdisciplinary teams	3+ physicians practicing together	3+ physicians practicing together	3+ physicians practicing together
Hours	Regular office hours + 3h/week extended hours	Regular and extended hours	Regular office hours + 3-5 session per week extended hours	Regular office hours + 3-5 sessions per week extended hours	Regular office hours + 3-5 sessions per week extended hours
Enrolment of Patients	Strongly encouraged	Strongly encouraged	Strongly encouraged	Commit to enrol patients	Commit to enrol patients
Allied Health		Already integral part of this team		Apply to Ministry of Health and Long Term Care to add other health professionals as part of a FHT.	Apply to Ministry of Health and Long Term Care to add other health professionals as part of a FHT.
After hours service for controlled patients	Variable	Variable	Nurse-staffed, Telephone Health Advisory Service	Nurse-staffed, Telephone Health Advisory Service	Nurse-staffed, Telephone Health Advisory Service
Pay	Fee for service	Blended capitation model [A] OR blended salary model [B] OR complement based remuneration [C]	Fee for service	Blended capitation model [A] – age and sex adjusted + bonuses and incentives	Blended capitation model [A] – complement based + bonuses and incentives

[A] Blended Capitation: Capitation based on a defined basket of primary care services provided to enrolled patients based on age/sex of each patient. Fee-for-service paid for other services [25].

[B] Blended Salary: Physicians are salaried employees of Community or Mixed Governance Family Health Teams: salary based on number of enrolled patients, plus benefits, bonuses [25].

[C] Complement based model: A base payment for a full-time equivalent "complement" in a given community/geographic area in addition to overhead payments, locum coverage, continuing medical education [25].

CONCLUSION

Fruitless negotiations between the Ontario government and the OMA have resulted in the government imposing unilateral cutbacks to health care in Ontario. Most of these cutbacks affect family physicians. Channelling new graduates into fee-for-service practices, as well as reducing their starting salaries may encourage them to practice out of province. Furthermore, existing family physicians in Ontario may be faced with difficulty as they try to meet higher patient care demands with decreasing gross incomes.

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Addressing Senior Immobility And Functional Decline During Hospitalization In Ontario

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ABSTRACT

There is a need to make Ontario hospitals more senior friendly, since hospitalization can put seniors at risk for unnecessary long-term functional decline. To achieve this end, the Council of Academic Hospitals in Ontario (CAHO) has recently introduced the Mobilization of Vulnerable Elders in Ontario project (MOVE ON), with the goal of improving mobility in hospitalized seniors. This article explains the evidence supporting early mobilization of seniors, while outlining the MOVE ON project and exploring the potential barriers to early mobility programs.

RÉSUMÉ

Il est nécessaire d'améliorer la manière dont nous traitons nos aînés dans les hôpitaux en Ontario car l'hospitalisation peut mettre les personnes âgées à risque de déclin fonctionnel à long terme. Pour parvenir à cette fin, le Conseil des hôpitaux universitaires de l'Ontario (CAHO) a récemment introduit le projet de mobilisation des aînés vulnérables en Ontario (MOVE ON), avec l'objectif d'améliorer la mobilité des personnes âgées hospitalisées. Cet article explique les éléments justifiant la mobilisation précoce des personnes âgées, tout en décrivant le projet MOVE ON et explore les obstacles potentiels à des programmes de mobilité précoce.

INTRODUCTION

A disproportionate amount of healthcare services are devoted to the elderly population. Although seniors represent 14.6% of the Ontario population, they account for nearly 50% of hospital costs and 56% of hospital days in the province [1,2]. To a certain degree, the high usage of healthcare services among seniors reflects the deleterious impact of hospitalization on senior health [3]. For instance, over 33% of seniors experience functional decline from hospital admission to discharge, defined as loss of independence with Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) [1, 4, 5]. Unfortunately, functional decline is frequently permanent, putting seniors at risk for re-hospitalization and admission into long-term care facilities, resulting in greater hospital usage and healthcare costs [1].

With this healthcare burden in mind, it is important to understand the factors associated with functional decline during hospitalization, since such an understanding represents the angle for change and improvement. One risk factor of particular significance is patient immobility [1]. In a study by Brown et al. (2009), seniors can spend up to 83.3% of hospital time in bed, with only 3.8% of time devoted to standing or walking [6]. Although bed rest is needed during recovery, these low levels of mobility can precipitate changes in functional independence through changes to the musculoskeletal and cardiorespiratory systems. Healthy seniors exposed to 10 days of continuous bed rest experienced a decline in aerobic capacity (VO2 max) that was equivalent to what would be expected from healthy aging over a period of a decade [5]. These same patients lost over 10% of muscle strength, even while following a meal plan that complied with weight-based macronutrient requirements. The decrease in strength and aerobic capacity is likely more profound in the setting of critical illness, since disease can contribute directly to a state of catabolism [5, 7]. Furthermore, organ reserve is decreased with age, such that declines in cardiorespiratory or musculoskeletal function are more likely to be clinically significant at an older age [1]. This can result in increased rates of nursing home placement [1, 3, 5, 6, 8] and longer hospital stays [3, 8]. Immobility is also associated with delirium, mood changes, constipation, orthostatic hypotension, and an increased risk for falls, atelectasis, aspiration pneumonia and deep venous thrombosis [7, 9]. It is significant to note that Brown et al. (2004) found that low levels of mobility were associated with high frequency of adverse outcomes even when controlling for illness severity, co-morbidities and pre-admission ADL levels [8]. This adds to the credence that mobility is an entity in and of itself that contributes directly to the discharged functional state of patients.

Keywords: Functional Decline; Senior Mobility; MOVE ON Project

ONTARIO SOLUTION: THE MOVE ON PROJECT

Given the association between immobility and adverse health outcomes, the Council of Academic Hospitals of Ontario (CAHO) has recently prioritized the issue of immobility in hospital settings [10]. In 2010, CAHO introduced the Adopting Research to Improve Care (ARTIC) program, with the goal of translating research evidence into actual practice [10]. One of the projects implemented by the ARTIC program concerns the early mobilization of seniors in acute care settings, known as MOVE ON (Mobilization of Vulnerable Elders in Ontario) [10, 11]. Although the project is currently ongoing, the primary outcome of MOVE ON is to improve the mobilization of senior patients in Ontario hospitals, with the secondary outcome of reducing hospitalization length of stay, decreasing long term care placement after acute care discharge, and improving functional status at discharge [1].
The project represents the practical application of previous research in favor of early mobilization programs. Prior studies have shown that early mobilization in acutely ill patients is associated with decreased hospital costs [12], less ICU days of delirium [13], greater functional scores at discharge [4], reduced nursing home placements at discharge [4], and improved subjective feelings of well-being [9]. As well, MOVE ON was initiated with the knowledge that early mobilization can be safely implemented even in the sickest of senior populations. A study by Bailey et al. (2007) on early mobilization in respiratory failure patients found that less than 1% of mobility activities were associated with adverse cardiorespiratory events [14]. In another study on mechanically ventilated patients, physical therapy was discontinued in 4% of cases because of low oxygen saturations and patient ventilator asynchrony [13]. In both these studies, the rate of adverse events was considered acceptable given the minor impact of these events in comparison to the positive outcomes experienced in other patients. The MOVE ON project hopes to expand on this research to demonstrate that early mobilization can be carried out safely and successfully on a larger scale.

BARRIERS TO MOBILITY AND AREAS FOR IMPROVEMENT

Although the direct outcomes of the MOVE ON project have not been published and the study is still ongoing, program coordinators have identified numerous barriers to early mobilization. For example, The Ottawa Hospital, as part of its project involvement, created focus groups composed of researchers, educators and front-line staff to determine barriers to mobilization [9]. These barriers included environmental challenges, as well as staff, patient and family perceived obstacles. According to the focus groups, patients can be restricted by a lack of personal motivation, a lack of knowledge regarding the benefits of early mobilization, and the presence of incapacitating symptoms such as weakness, fatigue and pain [9]. As well, healthcare workers responded that staff shortages and time constraints make it difficult to provide the assistance that is needed to deliver mobility activities, especially when hospitals are run on 8 am to 4 pm, Monday to Friday timetables [9]. Responses also indicated that hospital environments are not designed to encourage ambulation, since hospitals may lack assistive devices, exercise equipment, safety measures (railings and chairs in the hallway) and destinations of interest that are conducive to early ambulation [9]. These same barriers have been identified in other areas including Alabama by Brown et al. (2007) [15]. Additional barriers identified at MOVE ON sites and elsewhere include the feasibility and safety of early ambulation [9, 15, 16, 17, 18], especially in patient populations that use invasive devices (e.g. catheters) or are on continuous sedation [9, 19, 20].

To overcome these barriers, it is important to create a hospital culture that supports mobility. For example, MOVE ON coordinators have made it standard of care to ensure that mobility status is documented in every patient room, that mobility is addressed within 24 hours of admission and that mobility is a regular topic during team handover and patient rounds [9]. As well, MOVE ON has focused on ensuring that healthcare providers, family members and patients are educated about the benefits of early mobilization [9].

The participation of family members is an important avenue for change: the healthcare team at the SICU at the University of Michigan Health System saw improved compliance with mobility protocols when family members were educated about mobility, since it allowed them to act as educators, facilitators and coaches for their loved ones [21]. MOVE ON sites have also tried to create a physical environment more amenable to early mobilization. These efforts have included the provision of railings and chairs in hallways to promote safe mobility, as well as offering destinations of interest (e.g. social rooms) to encourage ambulation [9].

The importance of safety has figured prominently in the MOVE ON project. In order to promote both patient safety and full patient involvement, a tiered mobility protocol was developed by MOVE ON coordinators to ensure that mobility activities are introduced in a manner befitting patients' medical conditions [2]. Part of this thought process recognizes that mobility is more than just walking; even the simple act of sitting in a bed can be beneficial, since maneuvering to an upright position can improve ventilation and lung perfusion [14]. A tiered protocol may include such activities as turning or sitting in bed, standing, transferring from bed to chair, active and passive range of motion (ROM) exercises in bed or on a chair, and walking [2]. The MOVE ON protocol is based on determining the patient's best activity level using the ABC mnemonic: are they able to walk (Ambulate), can they transfer from bed to other positions like standing or sitting (Bed transfer) or can they not transfer positions (Cannot) [2]. Patients at level A can be encouraged to walk at least three times per day, patients at level B can be encour-

aged to transfer from bed to chair with active range of motion exercises at least three times per day, while patients at level C can be encouraged to have meals upright with active and passive ROM at least three times per day [2]. Although not explicitly part of the MOVE ON mandate, these protocols can include options such as neuromuscular electrical stimulation (NMES) [20], which may be used to elicit muscle contractions and mitigate muscle weakness in situations where traditional mobility activities (e.g. walking) may be difficult or unsafe (e.g. heavy sedation). The use of tiered mobility protocols has given MOVE ON healthcare workers the ability to develop personalized activity programs for patients of varying medical complexity.

CONCLUSION

Since 2010, with the introduction of the ARTIC program, Ontario has taken a great leap forward in ensuring research translation in the field of medicine. Previous research has shown a significant association between senior immobility and adverse health outcomes, including longer hospital stays and functional decline at discharge [1, 3, 5, 6, 8]. The MOVE ON project has been introduced across Ontario hospitals with the hope of successfully addressing the relationship between hospitalization, immobility and the functional decline of seniors. Although the outcomes have not yet been characterized, the project efforts have identified several barriers to early mobilization, including patient-related (e.g. incapacitating symptoms, lack of education), staff-specific (e.g. time restraints, safety concerns) and environment-based (e.g. lack of assistive devices) obstacles [9]. These barriers have shaped the early interventions of the MOVE ON program. A tiered mobility protocol has been adopted to ensure feasibility and patient safety [2]. The program has worked on establishing a culture of early mobilization by ensuring that mobility status is documented in patient rooms and is communicated during interdisciplinary rounds [9]. As well, the program has focused on educating all stakeholders about the importance of early mobility [9]. Hopefully, these interventions will prove fruitful in the long-term and ensure that Ontario hospitals support proper recovery and care.

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Promoting Physical Activity In Adolescent Cancer Survivors

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ABSTRACT

Self-management strategies, such as physical activity, have been identified to help young cancer survivors reduce or control the side effects that accompany modern cancer therapies whilst improving their overall quality of life. Despite the known benefits of physical activity, the majority of young cancer survivors are not meeting recommended guidelines. In this article, we discuss knowledge translation activities that are taking place across Canada to develop and disseminate resources to healthcare providers in an effort to improve physical activity counselling, and ultimately participation for adolescent cancer survivors.

RÉSUMÉ

Les stratégies d'auto-gestion, comme l'activité physique, ont été identifiées comme bénéfiques pour les jeunes survivants du cancer pour réduire ou contrôler les effets secondaires qui accompagnent les thérapies modernes du cancer, tout en améliorant leur qualité de vie globale. Malgré les avantages connus de l'activité physique, la majorité des jeunes survivants du cancer ne respectent pas les lignes directrices recommandées. Dans cet article, nous discutons des activités d'application des connaissances ayant lieu partout au Canada pour développer et disséminer des ressources aux fournisseurs de soins de santé dans un effort d'améliorer les conseils d'activité physique, et, ultimement, augmenter la participation des survivants adolescents du cancer.

INTRODUCTION

Progress in cancer treatment protocols offer hope for the 7,500 boys and girls aged 15 to 19 years living in North America who are diagnosed with cancer each year [1, 2]. Lymphomas, leukemias, germ cell tumours, central nervous system tumours, and melanomas are the most common types of cancers diagnosed in adolescents [1, 2]. Fortunately, recent survival estimates show that 80% will live for at least 5 years after their cancer is diagnosed [3, 4].

To assist this growing population of adolescent cancer survivors (i.e., adolescents who have been diagnosed with cancer, from the time of diagnosis onward [5]) on their survivorship journey, it is important to recognize the unique challenges they may face. Adolescence is a complex life stage associated with developmental demands that differ from those experienced during childhood and adulthood. Significant physical, psychological, and social challenges and changes characterize this phase in life [6]. As such, a diagnosis of cancer during adolescence may be particularly detrimental as it can interrupt boys' and girls' healthy development and thwart their ability to cope with the disease [7]. Indeed, many adolescent cancer survivors experience a host of adverse physical, psychological, and social side effects as a result of their treatment regimens (which may include a combination of surgery, chemotherapy, radiation, and/or hematopoietic stem cell transplant) [8-10].

In addition, it is estimated that 95% of young cancer survivors will develop at least one chronic health condition by the age of 45 years, and 80% will develop a serious, disabling, and/or life-threatening condition (e.g., pulmonary, cardiac, organ dysfunctions, neurocognitive impairment) as a result of their treatments [11]. Therefore, although they are 'cancer free', this population is far from 'disease free'. As well, young cancer survivors are 8.4 times more likely to die 5 years after their diagnosis compared to their healthy peers due to cancer recurrence and disease progression (57.5% of deaths), subsequent cancers (18.6% of deaths), and diseases of the circulatory (6.9% of deaths) and respiratory systems (2.6% of deaths) [12]. So while preventing cancer in the first place remains a top public health priority, a key challenge is to promote longevity, health, and quality of life amongst those diagnosed. For this reason, several researchers and stakeholders are focusing their efforts on helping young cancer survivors self-manage the negative side effects that may occur during treatment, immediately after, and/or years into survivorship. These

Keywords: Physical Activity; Counselling; Promotion; Adolescent Oncology

endeavours are necessary to empower adolescent cancer survivors and positively impact their overall health and quality of life [13].

PHYSICAL ACTIVITY AS A SELF-CARE STRATEGY

As researchers, we advocate for the use of physical activity as a self-care strategy to help adolescent cancer survivors address the negative side effects associated with the disease and its treatments, as well as help them enhance their health and quality of life throughout survivorship. Our focus on physical activity is based on the mounting evidence that it can improve physical, psychological, and social health amongst cancer survivors across the lifespan [14, 15]. It is also based on evidence that physical activity may help reduce the risk of several health conditions, such as cancer recurrence, co-morbidities (e.g., obesity, cardiovascular disease, second cancers, organ dysfunctions, neurocognitive impairment), and premature mortality [15-18].

Despite an abundance of evidence demonstrating the health benefits of physical activity, there are marked declines in physical activity participation amongst adolescents following cancer diagnosis, which generally remain low months, years, or decades into survivorship [19]. In fact, a recent study found that 65% of child and adolescent cancer survivors living in the United States were not meeting guidelines that recommend at least 60 minutes of physical activity daily [20]. As well, a recent review suggests adult survivors of childhood or adolescent cancers were less active than non-cancer controls [21]. These low rates may be due to the additional cancer-related barriers to physical activity experienced by adolescent cancer survivors, such as short- and long-term side effects, physical deconditioning, and overprotective attitudes of caregivers [22, 23]. Despite this, it should be noted that adolescent cancer survivors want information about physical activity [24] and are motivated to make positive lifestyle changes [25]. Therefore, finding ways to promote physical activity in this population is critical to enhance physical, psychological, and social health, and reduce morbidity and mortality.

HEALTHCARE PROVIDERS AS PHYSICAL ACTIVITY ADVOCATES

Given that adolescent cancer survivors experience close contact with their healthcare team during treatment and into survivorship, healthcare providers are in a key position to influence their patients' lifestyle behaviours through counselling. For instance, by conveying information about the importance of physical activity and prescribing it during clinic visits, adolescent cancer survivors may be more inclined to adopt an active lifestyle. Based on a recent systematic review, physical activity counselling may effectively enhance physical activity participation [26]. Although this conclusion is based on studies conducted with disease-free sedentary youth and adults [26], it points to the potential value of physical activity counselling in the cancer setting. In fact, emerging research performed with adult cancer populations has found that physical activity counselling led by healthcare providers is effective at increasing participation [27]. Considering that as many as 75% of adolescents agree with the statement "If my doctor told me to exercise I would do so" [28], physical activity counselling is likely to be effective in this population as well. Unfortunately, many adolescent cancer survivors living in North America are not receiving such counselling from their healthcare providers [24, 29].

Why is this the case? In adult cancer populations, insufficient resources (e.g., lack of money, time, and space), lack of expertise in the area of physical activity, and limited awareness of benefits of physical activity are key barriers to routine physical activity counselling in clinical practice [30]. In a similar vein, key barriers to physical activity counselling in pediatric cancer populations include a lack of knowledge and resources, as well as a belief that patients do not adhere to physical activity recommendations [31]. As such, equipping healthcare providers with information about the benefits of physical activity, providing them with evidence-based resources, and informing them that adolescents want this information, may increase the frequency of physical activity counselling in practice.

Recent recommendations by the National Comprehensive Cancer Network urge healthcare providers to give physical activity information to adolescent and young adult cancer survivors [32]. In doing so, there are special age-appropriate considerations that should be taken into account. In recognition of adolescents' growing desire to be independent and autonomous, every effort should be made to ensure that physical activity counselling is delivered to adolescent cancer survivors in a manner that is supportive, rather than controlling [33, 34]. Specifically, efforts should be made to counsel adolescent cancer survivors in a respectful, positive, non-judgmental way, and frame it as what they can do, versus what they cannot do [33, 34]. Further, some adolescents may be accompanied by their parents/guardians; in these instances care should be taken to give information directly to adolescents to facilitate feelings of autonomy and control [35].

TRANSLATING THE EVIDENCE: PLANS FOR ACTION AND EXISTING RESOURCES

To equip healthcare providers with the information they need to provide regular physical activity counselling to their patients, several groups are undertaking knowledge synthesis and resource development projects to translate knowledge into practice [36-39]. For example, we have synthesized the best available evidence from randomized controlled trials and controlled clinical trials exploring the effects of physical activity on health and quality of life outcomes with adolescent cancer survivors. In our

review, one randomized controlled trial and two controlled clinical trials met our inclusion criteria. Consequently, we are unable to determine whether physical activity has an effect on health and quality of life for adolescent cancer survivors given the very limited data and methodological limitations of the reviewed studies. Despite this, the studies included in our review provided evidence that physical activity is both safe and feasible. These findings are important as they can alleviate any concerns healthcare providers might have about the potential harm of physical activity during and/or after treatment for adolescent cancer survivors. We plan on publishing the results of our review to inform the scientific community of the safety of physical activity, as well as highlight the lack of research in this area. We also plan on presenting the findings to knowledge users (e.g., healthcare providers, adolescents). This work will be a useful starting point for the creation of physical activity information and resources such as pamphlets that will summarize our findings, as well as integrate guidelines and recommendations from other research and resources [36-39]. Lastly, this work will help lay the foundation for future studies and community outreach that aim to develop optimal physical activity programs for this population.

In addition to our own efforts, others have compiled evidence on the safety and benefits of physical activity, and used this evidence to develop critical resources and physical activity guidelines. For example, the Canadian Cancer Society provides a summary of the benefits of physical activity on their website and on print materials [39], and further recommends that cancer survivors follow nationally recognized physical activity guidelines developed by the Canadian Society for Exercise Physiology (CSEP) [37]. These guidelines, which were reviewed by healthcare providers, academics, international content experts, governmental and non-governmental organizations, and community members, encourage adolescent cancer survivors to engage in 60 minutes of physical activity daily [37]. Similarly, the American College of Sports Medicine and a team from the University of Calgary have developed evidence-based guidelines for adults [38] and younger (i.e., children and adolescents) cancer populations [36] respectively. In both cases, the guidelines were developed using rigorous processes that met international standards for guideline development.

Considering the current body of knowledge on the benefits of physical activity for cancer survivors and existing physical activity guidelines and resources, it is clear that adolescent cancer survivors can and should be engaging in physical activity. Special consideration should be taken with survivors on- and off-treatment, including carefully considering contraindications and co-morbidities that could interfere with cancer survivors' ability to perform physical activity (e.g., avascular necrosis, pulmonary disease, neurological problems, general performance limitations) [36, 40]. Furthermore, healthcare providers should take into account adolescents' past physical activity patterns, current levels of physical fitness, and activity preferences when recommending physical activity. They should also consider referring their patients to physical activity specialists (preferably specialists who have received training in cancer rehabilitation) [36-39]. Moving forward, the goal is to ensure healthcare providers use existing and emergent information and resources as tools for making physical activity recommendations for their patients, and incorporate physical activity counselling into routine preventive and rehabilitative cancer care.

CONCLUSION

A large and convincing body of evidence shows the benefits of physical activity for cancer survivors across the lifespan. Healthcare providers need to be made aware of this evidence so that they may confidently counsel adolescent cancer survivors to be physically active. It is hoped that the development of resources will provide healthcare providers with the knowledge and tools necessary to promote physical activity participation amongst adolescent cancer survivors, and thus reduce the burden of cancer on an already taxed healthcare system. Encouraging physical activity is the first step in helping the growing population of adolescent cancer survivors experience long-term health and enhanced quality of life.

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A New Way To Die

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On Friday, February 6th, 2015 the Supreme Court of Canada changed the way some Canadians can die. It struck down a twenty-two-year old ruling denying access to assisted-suicide by modifying the Criminal Code such that all adults who "clearly consent" and who suffer from a "grievous and irremediable medical condition (including an illness, disease, or disability) that causes enduring suffering and that is intolerable to the individual in the circumstances of his/her condition" can access assisted-suicide [1].

This decision remains controversial despite the fact that 68% of Canadians support the legalization of assisted-suicide, according to one recent poll conducted by the Environics Institute, a not for profit research group [2]. Advocates of people who suffer greatly due to medical conditions defined above are ecstatic and relieved, while advocates of vulnerable populations (e.g. health care professionals, Council of Canadians with Disabilities) and some individuals with disabilities condemn the decision. It is a question of balance between a person's autonomy and dignity and the need to protect vulnerable people from coercion into suicide. Twenty-two years ago, the Supreme Court decided that Sue Rodriguez's case was not strong enough to lift the ban on assisted-suicide.

THE ORIGINAL CASE

Rodriguez, who suffered from Amyotrophic lateral sclerosis (a progressive neurodegenerative disease resulting in loss of skeletal muscle control and eventually death), was effectively denied access to physician-assisted suicide [3]. At the time, this was determined based on the Canadian public's opinion about the sanctity of life and on the need to protect vulnerable people who might otherwise be persuaded into suicide. It is very difficult to know if someone is being pushed into an undesired death by the health system or by family members who may have vested interests. For example, a physician would not necessarily be aware if a family member is persuading the patient into suicide because of a large inheritance. Once assisted-suicide is accessible, it could easily lead to a slippery slope towards homicide of disabled and vulnerable people.

Keywords: Assisted-Suicide; End of Life; Physician-Assisted Suicide

THE CURRENT CASE

Kathleen Carter and Gloria Taylor challenged this ruling in 2011 by arguing that the previous decision was too broad. They claimed that, as such, it also prohibited access to assisted-suicide to those outside the class of vulnerable persons, who are competent, fully-informed, and not being coerced [1]. The challenge against this ruling in 2011 by Carter, 89, who suffered from spinal stenosis (narrowing of the spinal canal with spinal cord compression), and Taylor, 64, who suffered from ALS brought the Rodriguez case back into question. These women had poor prognoses and were fighting for the right to die peacefully and with dignity.

This time the Supreme Court found that the current legislature was too broad and created a "duty to live" precedent, which goes against the constitutional rights of life, liberty, and security of the person [1]. This "duty to live" is in direct contrast with the "right to live," and it challenges the legality of any consent to stop treatment and/or life-sustaining therapy (which is currently an accepted practice). They took heavily into consideration evidence from other countries that have legalized assisted-suicide, which showed that regulatory systems in Belgium, the Netherlands, and the state of Oregon, do manage to protect vulnerable people. It was also argued that legalization of assisted-suicide would avoid a dangerous black market of assisted-suicide either within Canada or abroad (assisted-suicide tourism). Furthermore, access to assisted-suicide would permit people to live longer, as opposed to them having to take their own lives while they are still capable. Lastly, it was argued that unregulated end-of-life practices in Canada such as palliative sedation and withholding or withdrawal of treatment are considered ethically acceptable by the Canadian public and are not ethically different from physician-assisted suicide. Despite these facts, however, many are concerned about the implications of allowing assisted-suicide in Canada.

Firstly, the wording of the ruling (seen above) has some people worried because it permits not only terminally ill patients, but also people suffering physically and/or emotionally, access to assisted-suicide. This level of permissiveness worries many people, including advocates of people with disabilities who believe

that allowing assisted-suicide will lead to a slippery slope toward murder, despite the safeguards that will be incorporated into the laws. There are two types of safeguards that can be employed: direct (i.e. restrictions in the legislation) and indirect (i.e. research on and development of alternatives to assisted-suicide). Interestingly, the United Kingdom's Supreme Court recently found that the evidence on the effectiveness of safeguards was not sufficient to draw any conclusions [1]. They also found evidence of failure to comply with safeguards and of an expansion of inclusion criteria for access to assisted-suicide as time passed after legalization, which presents the potential for a slippery slope (as in Belgium) [1]. Furthermore, qualified and experienced physicians will likely perform the assisted-suicide. This entails a question of medical ethics because their primary objective as a profession is to preserve life, not to actively end it. Another argument suggests that the development of palliative care would cease if assisted-suicide were legalized, thereby limiting options for those who wish to continue living. However, the judge rejected this argument based on evidence from the countries that have legalized assisted-suicide, which showed not only that vulnerable populations are not "at heightened risk of accessing physician-assisted dying", but also that in some places, palliative care improved after the legalization of physician-assisted dying.

WHAT IS NEXT?

The court ruling is suspended for 12 months, and during this time Canada will be drafting laws to better define who should have access to assisted-suicide, how they must gain this access, who will perform the procedure, and how to regulate the process in order to avoid potential abuse. Since health is under both Federal and Provincial jurisdiction, the regulation of assisted-suicide will likely be done at both these levels with input from physicians' colleges. Furthermore, Canada will need to investigate how other countries with legal assisted-suicide regulate and implement their laws.

Switzerland, in order to avoid coercion, allows assisted-suicide if the individual assisting the suicide does not have selfish motives (i.e. financial incentive or vengeance). This is an interesting point, as physicians are compensated financially for all procedures. How could one be sure that the physician is acting in the patient's best interest if it is more lucrative to perform an assisted-suicide than to keep the patient alive? Furthermore, under Swiss law, assisted-suicide is provided by giving the means to commit suicide (prescriptions), and euthanasia (injections) is not permitted [4]. Interestingly, it also permits assisted-suicide for foreign nationals. However, Canada is a different country with different challenges and all of the evidence must be considered with this in mind. It is important to note that many of the statistics available from these countries after which we may model our laws may not be truly representative of the situation. In Belgium, for example, roughly 50% of all cases of euthanasia were not reported to their Federal Control and Evaluation Committee [5], and therefore did not figure into their statistics.

Given the importance of informed consent with assisted-suicide, the legal definition of competence should also be revisited. At present, it is defined as being "able to understand the information that is relevant to making a decision about the treatment […] and able to appreciate the reasonably foreseeable consequences of a decision or lack of decision." If a person is found not competent, the decision made must be in keeping with the person's "best interests" [6]. It is difficult to define "best interests" in any situation, and the gravity of assisted-suicide may require more specificity.

Another important discussion that must be had is the degree of obligation of Canadian doctors in physician-assisted suicide. Will physicians volunteer to perform this procedure? Will there be clinics dedicated solely to physician-assisted suicide? A recent policy released by the College of Physicians and Surgeons of Ontario has implications about this. It states that the right of a physician to "limit the health services they provide for reasons of conscience or religion […] may impede access to care in a manner than violates patient rights under the Charter and Code" [7]. This implies that physicians may be obligated to play a role in assisted-suicide, even if it is just a referral. For many physicians, referring a patient to a clinic to die goes against their personal and/or religious convictions. There are no easy solutions to these issues, and there is significant work that needs to be done over the next year. Physician-assisted suicide will become an important discussion to have with family members over the next few years.

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Case Report: Type IV Paraesophageal Hernia Repair

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INTRODUCTION

Hiatus herniation refers to the transposition of the stomach through the esophageal hiatus of the diaphragm [1]. There are four types of hiatal hernia described [Figure 1]. A type I hernia is also referred to as a sliding hernia, as it may become spontaneously reduced to its normal position. These result from the widening of the crural diaphragm forming the esophageal hiatus and laxity of the phrenoesophageal membrane, causing the transient movement of the gastroesophageal (GE) junction out of the abdomen [1]. Type II hernias are unique and rare – these represent a true paraesopheal herniation of the fundus of the stomach into the chest, with the gastroesophgeal junction being appropriately located [1]. In types III and IV, the gastroesophgeal junction is abnormally positioned in the thorax. They are caused by laxity of the gastrosplenic and gastrocolic ligaments, leading to widening of the esophageal hiatus over time [2]. Type III, or a fixed intrathoracic stomach, is an incarcerated stomach. Type IV hernias are characterized by the presence of other viscerae, such as colon, small bowel or spleen within the hernia sac [2].

Most patients are asymptomatic or may present with reflux [3]. The most common presenting complaint in a patient with a large hiatus hernia is that of anemia – the hernia is found incidentally during endoscopic assessment for other sources of gastrointestinal bleeding [4]. More serious complications, warranting urgent/emergent surgical management, include gastric volvulus, outlet obstruction, hemorrhage or respiratory distress [2]. With gastric volvulus, patients will experience intermittent obstruction, causing symptoms of dysphagia and regurgitation [2]. Such patients are at increased risk of gastric ulcers, due to delay in gastric emptying and torsion of the stomach wall [2]. Perforation of these ulcers can lead to the emptying of gastric contents into the pleural, pericardial, or mediastinal spaces [2]. Further occult blood loss may occur with obstruction of venous return causing the stomach to become engorged and "weep" blood [2]. In some cases, impairment of circulation may be sufficient to produce necrosis and gangrene [2].

Surgical repair is commonly done laparoscopically, involving reduction of the hernia sac and its contents, followed by closure of the diaphragmatic defect. An esophageal lengthening procedure may be necessary to reduce chance of recurrence [2]. A relaxing diaphragmatic incision and prosthetic mesh reinforcement of the crurae may also be required for adequate closure of the defect, alone or in combination. The repair can also be performed via laparotomy or left thoracotomy.

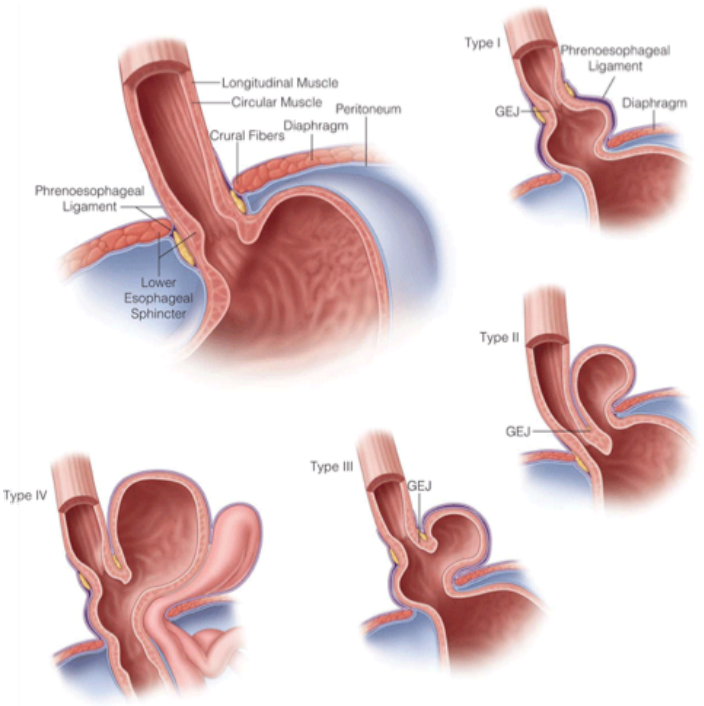

Figure 1. Normal anatomy of the esophageal hiatus shown with examples of different types of hiatal hernias [15].

Keywords: Hiatus Hernia; Hiatal Hernia; Paraesophageal Hernia; Congenital

CASE

The patient, a 43-year-old male, presented initially to the emergency department with persistent vomiting and epigastric pain. He was found to have a large incarcerated hiatus hernia. He had no previous complaints of retrosternal discomfort, heartburn, regurgitation or hematemesis. He was managed conservatively with a nasogastric tube decompression and discharged on a liquid diet.

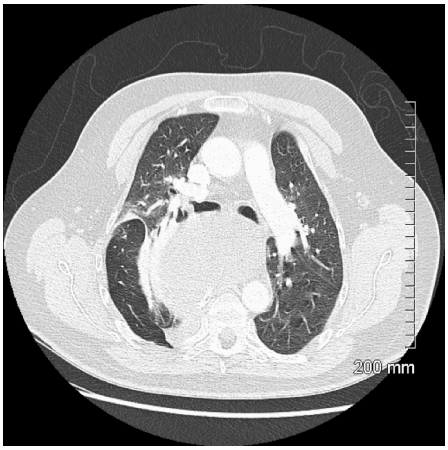

Figure 2. Pre-operative CT Axial View. The heart can be seen in the anterior chest. The left pulmonary artery can be seen towards the right to the image, while the ascending aorta and IVC are on the opposite side. The stomach lies within the thoracic cavity posterior to the heart, with the lesser curvature adjacent to the vertebrae and descending aorta.

His follow up included a CT scan [Figures 1, 2], which demonstrated a type IV paraesophageal hernia. The right-sided diaphragmatic defect measured approximately 16 cm at the widest point. Through this the entire stomach, along with several loops of ileum, the entire right colon, including the appendix and cecum, a portion of the transverse colon, spleen and intra-abdominal fat had herniated into the thoracic cavity. The CT also showed an organoaxial volvulus of the stomach, though not appearing to cause any inflammation or obstruction. A barium study [Figure 4] was also performed.

He was seen in follow up by Thoracic Surgery at the Ottawa Hospital, by which time he was asymptomatic and had resumed his previous diet. The decision was made not to proceed with elective surgery, given the patients absence of symptoms and the lack of obstruction of any of the herniated viscera. However, the patient subsequently presented to the ER approximately 2 months later, with a one-day history of vomiting and epigastric pain, similar to the initial ER visit. He was managed conservatively and discharged after 4 days, but was scheduled for a hernia repair and fundoplication within a month.

The surgical repair proceeded without complication. However, the decision was made to convert from a laparoscopic to open procedure due to lack of adequate exposure. Reduction of several loops of small bowel, as well as the cecum and appendix was achieved before the conversion to an open procedure was made via a midline incision. The unusual position of the cecum in the midline amongst loops of small bowel was taken as evidence for a congenital malrotation. The hernial sac was separated completely from the mediastinum using a combination of harmonic and blunt dissection. Sutures were placed on three fronts to close the hiatus, at its left and right lateral aspects and the posterior aspects of the crura. A bioabsorbable mesh was also used

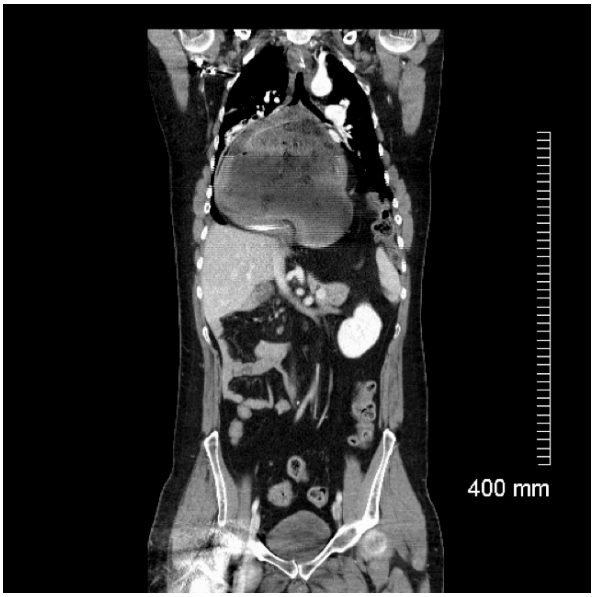

Figure 3. Pre-operative CT Coronal View. Note the large herniation of abdominal contents into the thoracic cavity. The hernia sac sits towards the patient's right side above the liver, adjacent to airspace. The herniation includes the stomach, proximal to the gastric antrum and the small bowel distal to the descending duodenum.

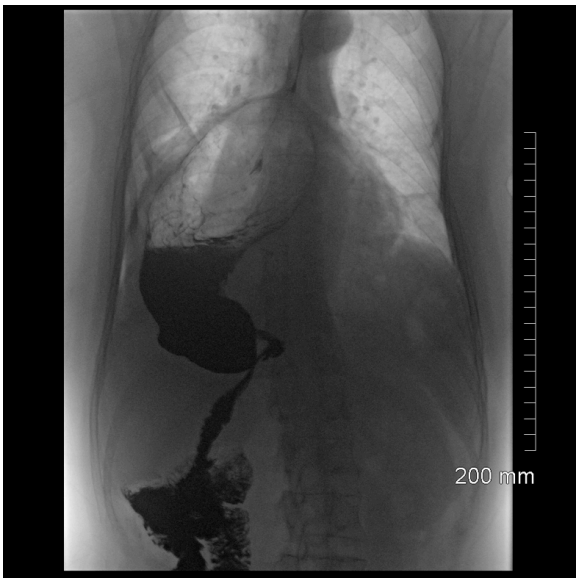

Figure 4. Pre-operative Barium Study. The stomach is seen in the thorax in organoaxial volvulus, causing partial obstruction. Note the barium preparation collecting towards the antrum.

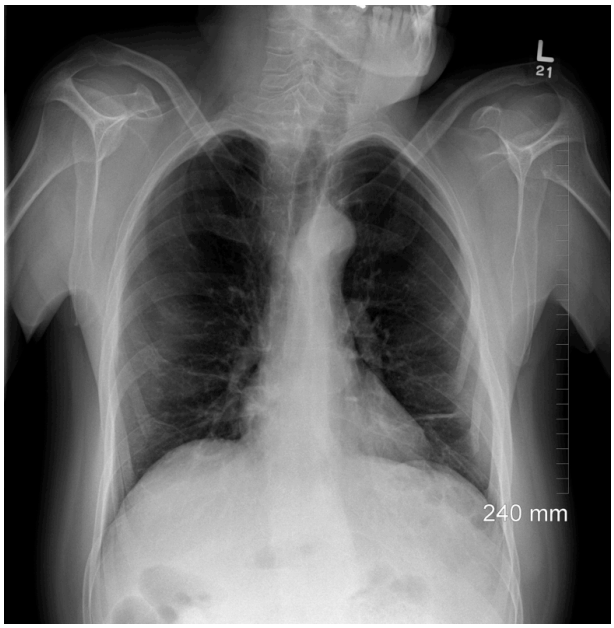

Figure 5. Post-operative Chest X-ray. In contrast to the pre-op imaging, the stomach is no longer in the thorax.

to reinforce the left crus. As an adequate length of intra-abdominal esophagus was achieved, it was felt unnecessary to perform a fundoplication. However, a gastrostomy tube and sutures were used to straighten the greater curve of the stomach and anchor it to the abdominal wall.

Post-operatively, there were no major complications. A barium study showed no leak in the esophagus. The patient appeared to have gastroparesis (delayed gastric emptying in absence of mechanical obstruction), with the barium being retained in the stomach. A gastrostomy tube was placed as a precaution. This is a well documented complication of gastric and esophageal surgeries, resulting from a stretch injury [5]. This was successfully treated prior to discharge with metoclopramide, which functions to increase gastric motility through antagonism of dopamine receptors in the gut [6]. While the patient did develop wound infection at the site of the gastrostomy tube, no symptomatic or radiological evidence of recurrence was seen six months post-operatively [Figure 5].

DISCUSSION

Aside from the degree of severity, there are a few other unique aspects to this case that merit comment. Age is a well-known risk factor for hiatus hernia. A review of paraesophageal hernia repairs at the Mayo Clinic reported an average age of 72 at presentation [7]. The relatively young age of the patient suggests that this defect may have at least begun as a congenital deformity. In addition to mild cognitive impairment and the previously mentioned intestinal malrotation, the patient presented with other congenital abnormalities including agenesis of the right kidney and fusion of the posterior elements of T2-T4 vertebrae, both asymptomatic and found incidentally on the pre-operative CT [Figure 3]. These findings do not fit any classic descriptions of genetic syndromes.

The management of the patient was in line with recommended practices, which consist of initial medical management with surgical repair reserved for urgent/emergent complications or refractory symptoms. The patient presented twice with apparent gastric outlet obstruction, which was twice resolved non-operatively, before the surgery was done electively. In general, surgical correction is recommended in symptomatic patients to prevent serious complications. There was certainly a risk of gastric ischemia in this patient, given the presence of volvulus.

The anatomical presentation and surgical repair are fairly straightforward, but there are some less intuitive points worth mentioning. The patient's stomach was seen in an organoaxial rotation on CT. This is the typical presentation of gastric volvulus in paraesophageal herniation, especially where the GE junction is still fixed to the diaphragm, in which the stomach rotates around the longest axis (from the GE junction to the pylorus) [8]. Mesentericoaxial rotation is less common, occurring around an axis bisecting the lesser and greater curvatures, so that the posterior surface of the stomach ends up facing anteriorly [8].

There are several important surgical considerations. Firstly, the importance of dissecting the hernia sac from the mediastinal structures, which is thought to facilitate intraoperative reduction by releasing the esophagus from any adhesions and has been shown to reduce the risk of early recurrence [9]. Full sac excision is commonly done, as well [9]. One case series has shown decreased early recurrence with sac excision, though it may be technically difficult in the repair of large hernia defects and some concern has been raised about the increased potential for vagal injury, leading to such complications as gastroparesis [9, 10]. In this case, where the sac was fully excised, the patient's apparent gastroparesis did not persist beyond several days post-operatively, suggesting vagal nerve stretch as a causative factor.

A second point is the importance of closing the diaphragm without tension, especially in the presence of attenuated crura. This attempts to reduce the risk of recurrence via reopening of the defect and is often achieved using a biological mesh, which may be used to cover the defect itself (minimizing tension) or, as in this case, to reinforce to crura [11, 12]. The use of mesh is recommended for large defects and has been shown to reduce the risk of short-term recurrence [11]. An incision into the diaphragmatic crura may also be necessary to relieve tension [13]. A fundoplication is typically done with a hiatus hernia repair, serving the dual purpose of blocking any transposition of structures through the repaired defect and strengthening the LES to prevent acid reflux [14]. It was not felt to be necessary in this case, given that the length of the esophagus was sufficient

and was not likely to have played a role in the initial herniation. However, a gastrostomy tube was used to maintain the position of the stomach and prevent recurrence of volvulus.

This case details a complicated presentation of a relatively common condition. The anatomical defects are remarkable, given a rather insidious, somewhat non-specific presentation. In addition to being technically interesting, this case highlights some of the important aspects for the surgical management of such patients.

CONSENT

Oral consent was obtained from both the patient and his caretaker during follow up and is documented in the patient's chart.

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Efficacy Of Inhaled Corticosteroids For Patients With Asthma: A Descriptive Review Of Randomized Controlled Trials

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ABSTRACT

Objective: To evaluate the efficacy of inhaled corticosteroids (ICS) in patients with asthma based on changes in sputum eosinophil counts, through a review of relevant randomized controlled trials (RCTs).
Methods: Studies were retrieved from MEDLINE, EMBASE, the SYSTEM FOR INFORMATION ON GREY LITERATURE, and the INSTITUTE FOR SCIENTIFIC INFORMATION from February 1, 2003 to February 1, 2013 based on a comprehensive search strategy. Articles were screened through two stages: title and abstract, and full-text screening. Inclusion criteria included: RCT-type study, asthma population, ICS intervention, and change in sputum eosinophils as an outcome. Exclusion criteria included: other therapies combined with ICS, allergen challenge within intervention, and non-English studies. Following screening, data extraction, and quality appraisal, a descriptive synthesis of trials was conducted.
Results: The search strategy retrieved 447 articles, of which 66 underwent full-text screening, and of which 37 RCTs met the inclusion criteria. The included articles utilized the following types of ICS: budesonide, fluticasone propionate, ciclesonide, beclomethasone dipropionate, and mometasone. Of 46 intervention groups across the trials, 22 demonstrated a statistically significant ($p < 0.05$) reduction in sputum eosinophil counts.
Conclusion: There is insufficient evidence to suggest the superiority of one ICS treatment over another. Further research needs to be conducted to evaluate the relative impact of ICS products upon eosinophil counts, as well as clarify what measurable change in baseline eosinophil counts is required to observe a change in symptom improvement and disease control.

RÉSUMÉ

Objectif: évaluer l'efficacité des corticostéroïdes inhalés (CSI) chez les patients souffrant d'asthme en fonction des changements dans les numérations d'éosinophiles des expectorations, par une revue d'essais contrôlés randomisés (ECR) pertinents.
Méthodes: Des études ont été récupérés à partir de MEDLINE, EMBASE, le SYSTEM FOR INFORMATION ON GREY LITERATURE, et l'INSTITUTE FOR SCIENTIFIC INFORMATION du 1er février 2003 au 1er février 2013, par le biais d'une stratégie de recherche exhaustive. Les articles ont été examinés en deux étapes: par titre et résumé, et par consultation du texte intégral. Les critères d'inclusion incluent: une étude de type ECR, une population avec asthme, une intervention avec CSI, et un changement dans les éosinophiles d'expectorations en tant que résultat. Les critères d'exclusion incluent: d'autres thérapies combinées avec les CSI, une provocation allergénique durant l'intervention, et des études de langues autres que l'anglais. Après le dépistage, l'extraction de données et l'évaluation de la qualité, une synthèse descriptive des études a été menée.
Résultats: La stratégie de recherche a récupéré 447 articles, dont 66 ont subi un dépistage en texte intégral, et dont 37 ECR ont répondu aux critères d'inclusion. Les articles utilisés ont utilisé les types de CSI suivants: budésonide, propionate de fluticasone, ciclésonide, dipropionate de béclométhasone et mométasone. Parmi les 46 groupes d'intervention entre les études, 22 d'entre eux ont démontré une réduction statistiquement significative ($p < 0,05$) des éosinophiles des expectorations.
Conclusion: Il n'existe pas suffisamment de preuves pour suggérer la supériorité d'un traitement par CSI par rapport à un autre. D'autres études doivent être menées pour évaluer l'impact relatif des produits de CSI sur le compte d'éosinophiles, ainsi que pour clarifier quel changement mesurable des éosinophiles de base est nécessaire pour observer un changement dans l'amélioration des symptômes et dans le contrôle de la maladie.

Keywords: Asthma; Sputum Eosinophils; Inhaled Corticosteroids; Chronic Disease Management

BACKGROUND

Asthma is characterized by variable airflow limitation, which is detected by measurements of airway responsiveness such as spirometry [1]. This pulmonary disease is also associated with airway inflammation, which is manifested by an increased number of eosinophils in the bronchial tissues and secretions [2]. Inhaled corticosteroids (ICS) are considered first-line anti-inflammatory therapy for asthmatic patients [3]. These ICS act to alter gene production involved in the inflammatory process, reducing the synthesis of inflammatory proteins and cytokines. Corticosteroid therapy has been shown to reduce the number of inflammatory cells and their inflammatory action, basement membrane thickness and airway hyperresponsiveness [4].

The most comprehensive, non-invasive method of measuring the severity of airway inflammation is through induced sputum cell count analysis. Specifically, the sputum induction technique is common, and reported as reliable, and valid [5]. Moreover, sputum eosinophilia, recognized as a trademark of asthma evaluation, has been shown to predict the response to corticosteroid treatment. Generally, sputum eosinophil counts decline within three to seven days following the initiation of ICS in the majority of patients requiring treatment [6]. As a result, induced sputum cell counts for management of asthma are more frequently used. Clinical studies have found that using ICS treatments to cause sputum eosinophil counts to fall within a normal range resulted in significant reductions in asthmatic exacerbations. Evidently, sputum cell count analysis can play a prominent role in optimizing the management of asthma in clinical practice [6].

The most recent reviews conducted by Rank et al. [7] and Gan et al.[8] both investigated the use of ICS in asthma and chronic obstructive pulmonary disease, respectively. However, there are gaps left by studies in the literature that this review will bridge. Specifically, there have not been any published systematic reviews specifically investigating the effects of ICS on sputum eosinophils in patients with asthma.

The primary goal of this review is to evaluate the efficacy of ICS in patients with asthma based on changes in sputum eosinophil counts through a review of relevant randomized controlled trials (RCTs) over the past 10 years.

METHODS

Eligibility Criteria and Literature Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this review, although our protocol was not registered [9]. Prior to article retrieval, a comprehensive search strategy was developed in conjunction with a research librarian for the purpose of identifying all relevant studies. A search was conducted with the proposed strategy to identify randomized controlled trials (RCTs) involving patients with asthma, of any age, placed on an inhaled corticosteroid (ICS) intervention. RCTs including an ICS intervention in combination with other concurrent treatments were not included, as the purpose of the review is to solely investigate the specific effect of ICS on asthma patients. Studies included in the review were also required to conduct sputum induction as a part of their procedure, and more specifically to report on the change in sputum eosinophil count pre- and post-intervention, as this was the main outcome of the primary objective of this study. Studies measuring the effect of ICS on patients with asthma following an allergen challenge were excluded as the presence of the allergen challenge was a confounding factor to our outcome of interest, resulting in increased sputum eosinophils. Finally, non-English articles were excluded, as translators were not recruited for this project. In summary, inclusion criteria for the review included the following: RCT-type study, asthma population, ICS intervention, and change in sputum eosinophils as an outcome. Moreover, exclusion criteria for the review included the following: other therapies combined with ICS, allergen challenge within intervention, and non-English studies.

The review was conducted on English-language articles found through searches of MEDLINE, EMBASE, the SYSTEM FOR INFORMATION ON GREY LITERATURE (SIGLE), and the INSTITUTE FOR SCIENTIFIC INFORMATION (ISI). The search was conducted from February 1, 2003 to February 1, 2013. Only RCTs conducted in the past 10 years were included in order to strictly investigate the most recent ICS interventions being used to treat patients with asthma. To ensure that a comprehensive search strategy was being used for these databases, several different variations of the strategy were tested to investigate any potential changes in the number of retrieved articles. The search strategies tested can be found in Supporting Information S1.

Study Selection

Following the removal of duplicate articles, two reviewers (MA & AA) independently evaluated the eligibility of all of the retrieved articles that resulted from executing the search strategy. A pilot-tested screening form (found in Supporting Information S1) was developed for evaluating the retrieved studies. This form outlined the criteria that each article had to meet to move on to subsequent stages of screening, and finally, to data extraction. The first stage of screening conducted by the reviewers involved title and abstract review. Articles that moved forward to the next stage of screening either fulfilled all three criteria outlined, or did not present enough information in their title and abstract to be evaluated based on the screening form. The three criteria were the following: the study involves sputum induction and reports eosinophil count as an outcome; the study is an RCT with human subjects; and, the study investigates patients with asthma undergoing an ICS treatment. During the second stage of screening, the reviewers conducted a full-text review of the

articles that had passed the first level. Once again, each article was evaluated based on the criteria of the screening form. Articles that met all three criteria moved forward to the data extraction stage. Disagreement was resolved by consensus at each stage of screening. Chance-corrected pre-consensus agreement was measured at both the title and abstract as well as full text screening stages using the kappa statistic. Values of 0 to 0.20 represented slight agreement, 0.21 to 0.40 represented fair agreement, 0.41 to 0.60 represented moderate agreement, 0.61 to 0.80 represented substantial agreement, and greater than 0.80 represented almost perfect agreement [10].

Data Extraction

Following screening, the two reviewers (MA & AA) independently used a standardized data extraction form (found in Supporting Information S1). Information on the patient demographics for each article was extracted, including age, number of enrolled patients, gender ratio, asthma severity, and forced expiratory volume (FEV1) baseline measures. Moreover, the treatment regimen, consisting of dose and type of ICS used during the intervention, as well as the duration of treatment, was also identified for each article. Finally, information regarding the sputum induction procedure and sputum eosinophil measures was collected for each article. Disagreement between the two reviewers was resolved by consensus and consultation of a neutral third individual (MD & JJR) used in instances where both reviewers could not agree.

Assessment of the risk of bias

Two reviewers (MA & AA) independently assessed the risk of bias for each included study using the Cochrane Risk of Bias Tool [11]. Disagreement between the two reviewers was resolved by consensus. Each article was evaluated based on risk of bias for the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. For a study that reported a low risk of bias for all the criteria, it was unlikely that any plausible bias would seriously alter the results. For a study that reported an unclear risk of bias for one or more of the criteria, any plausible bias would raise doubt about the results. For a study that reported a high risk of bias for one or more of the criteria, any plausible bias would seriously weaken confidence in the results [11].

RESULTS

The initial search conducted in MEDLINE, EMBASE, and ISI using the comprehensive search strategy produced 447 results. Following the removal of 90 duplicate articles, title and abstract screening was conducted for 357 unique citations. After this first stage of screening, 66 articles met the criteria for the next stage (estimated kappa = 0.84). Full-text screening was then conducted on these remaining articles; 29 of the 66 articles were excluded [12-40]. Primary reasons for exclusion included: lack of randomization, combination of ICS with other treatments, the use of allergen challenge, and a lack of set treatment dose of patient cohorts. Two of the 29 articles were excluded because they were written in Chinese [13] and Japanese [33]. In total, 37 articles met the inclusion criteria and went on to data extraction (estimated kappa = 0.85) [41-77]. Figure 1 illustrates the PRISMA flow diagram summary of the review process. No unpublished studies met the criteria for inclusion in this review. The 37 articles were assessed for risk of bias [11], and six articles had a low risk of bias [43,57,70,75-77], 17 had an unclear risk of bias [42,46,47,52,53,55,56,58,61,63-66,69,71-73], and 14 had a high risk of bias [41,44,45,48-51,54,59,60,62,67,68,74]. Detailed results for the risk of bias assessment of each article can be found in Supporting Information S1.

The included articles utilized the following types of ICS: budesonide, fluticasone propionate (FP), ciclesonide, beclomethasone dipropionate (BD), and mometasone. Table 1 provides a summary of the number of reviewed studies according to ICS treatment. The results for each of the ICS are provided in Tables 2-6; the author, sample size, age, asthma severity, predicted FEV1% predicted at baseline, dose, duration, eosinophil count, and risk of bias is reported for each of the included studies. Table 2 provides a summary of budesonide studies [42-56], in which nine of 16 intervention groups demonstrated a statistically significant ($p < 0.05$) decrease in sputum eosinophil count [43-46,48,50,51,53,54]. Table 3 provides a summary of the FP studies [41,57-67], in which five of 14 intervention groups dem-

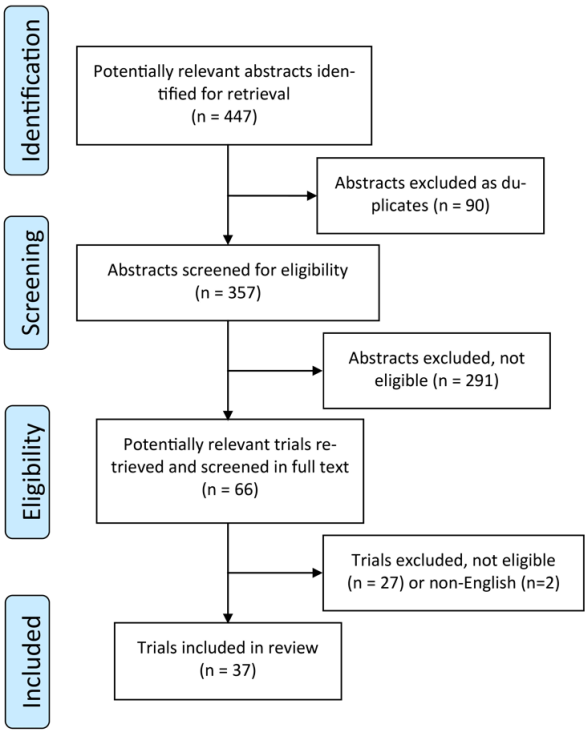

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing stages of systematic review of randomized controlled trials for effectiveness of inhaled corticosteroids on sputum eosinophilia among asthmatic patients.

Table 1. Summary of RCTs based on treatment

ICS Treatment	Number of RCTs Reviewed
Budesonide[42-56]	15
FP[57-67]	11
Ciclesonide[68-72]	5
BD[73-75]	3
Mometasone[76,77]	2
FP or Ciclesonide[41]	1

* Statistically Significant ($p < 0.05$); NS – Not significant;
ICS – Inhaled corticosteroids; RCT – Randomized controlled trial;
FP – Fluticasone propionate; BD – Beclomethasone dipropionate

onstrated a statistically significant ($p < 0.05$) decrease in sputum eosinophil count [58,62-65]. Table 4 provides a summary of ciclesonide studies [41,68-72], in which four of nine intervention groups demonstrated a statistically significant ($p < 0.05$) decrease in sputum eosinophil count. Table 5 provides a summary of BD studies [73-75], in which three of five intervention groups demonstrated a statistically significant ($p < 0.05$) decrease in sputum eosinophil count. Table 6 provides a summary of mometasone studies [76,77], in which one of two intervention groups demonstrated a statistically significant ($p < 0.05$) decrease in sputum eosinophil count [76].

DISCUSSION

This review is unique in that it is the first to investigate RCTs on asthmatic patients receiving ICS and reporting sputum eosinophilia outcomes. It reports on the status of efficacy of more recent ICS treatments in the last 10 years. In evaluating the significance of changes in sputum eosinophil counts, it is important to account for the baseline sputum eosinophil measures for all of these patient groups. There was considerable variation in the reductions in sputum eosinophilia within the same treatments and even under the same doses; this may be attributable to differences in baseline patient sputum eosinophils.

Eosinophilic asthma is characterized by a sputum eosinophil proportion greater than 2% [78], and we do not expect that ICS treatments would be effective in significantly reducing sputum eosinophilia in asthmatic patients that fall below this threshold, as this would be considered a non-pathological level. Since the baseline eosinophil count for each study is a mean of the treatment group, we cannot say that any one set of patients consists completely of patients with eosinophilic asthma, or does not contain any of them. However, the mean baseline value can be used as an indicator of what proportion of eosinophilic asthmatic patients we can expect in a treatment group. Ideally, we would see a significant reduction in sputum eosinophila in patient groups with higher baseline measures for an effective ICS treatment. On the other hand, we anticipate that the baseline values of non-eosinophlic asthmatic patients remain stable for the same treatment. It should be noted that even if the mean baseline sputum eosinophil values falls just above the 2% threshold, it may still contain a significant proportion of non-eosinophilic asthmatic patients. This may skew the results leading to a non-significant change in sputum eosinophilia.

Of the 46 total intervention groups included in this review, 22 demonstrated statistically significant decreases in sputum eosinophils. Within these 22 treatment groups, 20 presented a mean baseline measure greater than the 2% eosinophilic asthma cut-off, one presented a value below the 2% cut-off, and two groups did not report the mean baseline eosinophils. In contrast, the 24 groups with a non-significant change in sputum eosinophils showed 16 of them to be above the 2% cut-off for eosinophilic asthma, six of them to be below the cut-off, and two without reported mean baseline eosinophils. However, six of the 16 groups above the 2% cut-off were still fairly close to this threshold, reporting sputum eosinophil values below 3%. These results may indicate greater efficacy of ICS reduction of sputum eosinophils more specifically in the eosinophilic subset of asthma. Moreover, the treatment durations for four intervention groups in studies Gauvreau et al. [69] and Erin et al. [70] ranged from five to seven days each; these studies had the shortest treatment duration of all included RCTs in this review. This shorter treatment period may have contributed to the non-significant change in sputum eosinophils. Finally, the results of Menezes et al. [49] should be interpreted with caution, as there was a severe imbalance in the loss to follow-up between the two treatment groups; eight of 19 patients were lost in one group, while only one of 13 patients were lost in the other group.

Limitations

There are several limitations to this review of the literature. First, due to heterogeneity in the doses, durations, and baseline sputum eosinophil measures, the resulting changes in sputum eosinophilia were not pooled in meta-analysis for the individual ICS treatments. Furthermore, another minor issue deterring the authors from pooling the results was a lack of reporting quantitative changes in sputum eosinophilia. Also, study authors were not contacted for missing data. Only English articles were included, although only 2 non-English articles were identified during screening and would therefore be unlikely to significantly affect our conclusions.

Another limitation of this review is the method by which the efficacy of the drug was evaluated. For the purposes of this paper, an RCT that reported a statistically significant decrease in sputum eosinophilia indicated that the ICS in question was effective. However, this statistical significance does not necessarily equate to clinical significance. That is to say, a small change in sputum eosinophilia may result in a statistically significant difference, but it may not be sufficiently beneficial to the patient to warrant a change in clinical practice. Ideally, a clinically significant thresh-

old of change from baseline eosinophil counts may be identified that consistently translates into measurably improved clinical outcomes, such as the FEV1, for patients with asthma, leading to improved disease management.

In addition, some ICS treatments were missed because RCTs published only in the last 10 years were investigated [7]. For example, Condemi et al. [79] and Lazarus et al. [80] both tested triamcinolone, an alternative ICS that was not evaluated in this review, since it fell outside the 10-year period. However, considering there have not been recent studies published on triamcinolone, and other ICS not included in the review, it can be inferred that they are no longer considered first-line ICS treatments due to more effective medications being available. Given that the goal of this review was to evaluate the most recent ICS treatments for patients with asthma, studies such as the ones on triamcinolone fall outside the scope of this paper. In future studies, it would be beneficial to also evaluate ICS in combination therapies as this is often the case in the clinical setting and thus would improve external validity. The risk of bias in the included RCTs for this review also proved to be a potential limitation. Of the 37 studies included, only six had a low risk of bias, with the remaining studies either having an unclear or high risk of bias. Consequently, the results of these studies should be interpreted with caution.

Finally, given that this review investigated changes in sputum eosinophilia as the primary outcome, we were limited on the population of asthmatic patients that we could investigate. As previously discussed, in patients with non-eosinophilic asthma, we would not expect a significant reduction in sputum eosinophilia. As such, a potential option for this review would have been to focus strictly on eosinophilic asthmatics. However, most studies only reported mean baseline sputum eosinophil measures, and did not report on whether all patients were greater than the 2.0% threshold. Thus, we used the mean baseline values as an indicator for the individual patients, but were aware that there may have been significant variation within the patient groups.

CONCLUSION

This study discussed the effects of ICS on sputum eosinophils in asthma patients; however, the clinical relevance is uncertain. There is insufficient evidence to suggest the superiority of one ICS treatment over another. Further research needs to be conducted evaluating the relative impact of ICS products upon eosinophil counts, as well as in clarifying what quantitative level of change in baseline eosinophil counts is required to observe a change in symptom improvement and disease control. Ideally, the further research in this field would include more high quality studies with low risk of bias in concordance with the Cochrane Risk of Bias Tool [11], and a meta-analysis of all trials evaluating ICS treatments.

Table 2. Summary of Budesonide ICS RCTs

Author (year)	Intervention group sample size	Mean Age	Asthma Severity	FEV_1 % predicted at baseline	Dose (µg)	Duration	Mean baseline eosinophil count	Mean change in eosinophil count	Risk of bias
Green et al. (2006)[42]	49	42	Persistent	74.8	200 800	4 weeks	2.8% 2.7%	-0.3% -1.1%	Unclear
Kelly et al. (2010)[43]	14	29	Mild, stable	82.2	400	11 days	2.5%	-1.5% *	Low
Hoshino et al. (2012)[44]	13	29	Mild to moderate, persistent	77.9	400	24 weeks	5.2%	-0.6%*	High
Basyigit et al. (2004)[45]	10	42	N/A	89.5	400	2 weeks	18.0%	-9.0%*	High
Hauber et al. (2006)[46]	9	35	Mild	90.2	800	4 weeks	9.7%	-2.0%*	Unclear
Barnes et al. (2007)[47]	38	45	Persistent	73.6	1600	4 weeks	0.5%	+0.2%	Unclear
Rytila et al. (2004)[48]	39	7	Mild, persis-tent	90.9	800 (4 weeks); 400 (20 weeks)	24 weeks	6.0%	-4.0%*	High
Menezes et al. (2008)[49]	10	43	Moderate to severe	81.2	800	9 weeks	8.2%	-5.3%	High
Perng et al. (2004)[50]	21	45	N/A	83.0	1200	6 weeks	16.8%	-10.2%*	Hight
Echevarria et al. (2011)[51]	33	26	Mild to severe	89.5	800	6 weeks	28.0%	Decrease*	High
Strauch et al. (2003)[52]	25	10	N/A	97.0	400-800	4 weeks	1.6%	-0.6%	Unclear
Maneechotes-uwan et al. (2010)[53]	25	52	Stable	85.5	200	8 weeks	12.5%	-6.3%*	Unclear
van Dalen et al. (2009)[54]	34	39	Mild to mod-erate	89.5	400	6 weeks	N/A	Decrease*	Unclear
Boulet et al. (2009)[55]	14	35	Mild	87.4	800 (2 weeks); 1600 (1 week)	3 weeks	2.4%	-1.4%	Unclear
Maneechotes-uwan et al. (2007)[56]	12	38	Moderate, persistent	72.3	800	10 weeks	4.8%	-4.5%	Unclear

* Statistically Significant ($p < 0.05$); NS – Not significant; ICS – Inhaled corticosteroids; RCT – Randomized controlled trial; FEV1 – Forced expiratory volume in 1 second; µg – Microgram

Table 3. Summary of FP ICS RCTs

Author (year)	Intervention group sample size	Mean Age	Asthma Severity	FEV_1 % predicted at baseline	Dose (µg)	Duration	Mean baseline eosinophil count	Mean change in eosinophil count	Risk of bias
Belda et al. (2007)[57]	19	39	Moderate	69.0	4000	24 hours	13.0%	-6.6%	Low
Kawayama et al. (2008)[58]	11	27	Mild, stable	97.7	400	2 weeks	12.2%	-4.8%*	Unclear
Hoshino et al. (2009)[59]	14	43	Mild, persistent	87.0	200	8 weeks	5.1%	-0.7%	High
Hozawa et al. (2009)[60]	12	50	Stable	84.4	200/400/800	4 weeks	11.4%	+0.7%	High
Giannini et al. (2003)[61]	9	35 40	Stable	100.5 104.5	250 100	12 weeks	1.9% 3.3%	-0.3% -2.0%	Unclear
Kanazawa et al. (2007)[62]	15	36	N/A	90.5	400	12 weeks	12.1%	-11.3%*	High
Di Franco et al. (2006)[63]	18	43	N/A	90.1	1000	2 weeks	38.0%	-35.0%*	Unclear
Koopmans et al. (2006)[64]	27	32	Moderate to moderate, persistent	89.9	500	4 weeks	3.2%	-2.4%*	Unclear
Jayaram et al. (2005)[65]	18	35	Persistent	72.0	250	8 weeks	11.9%	-10.2%*	Unclear
Foresi et al. (2005)[66]	18 17	38 34	N/A	83.8 88.8	1000 200	6 weeks	16.4% 16.7%	-15.4% -13.9%	Unclear
Bacci et al. (2012)[67]	10	42	Mild to moderate	92.6	250	24 weeks	<3.0%	NS	High
Hoshino et al. (2010)[41]	16	45	Mild, persistent	98.6	200	8 weeks	11.8%	-1.0	High

* Statistically Significant ($p < 0.05$); NS – Not significant; ICS – Inhaled corticosteroids; RCT – Randomized controlled trial; FEV1 – Forced expiratory volume in 1 second; µg – Microgram

Table 4. Summary of Ciclesonide ICS RCTs

Author (year)	Intervention group sample size	Mean Age	Asthma Severity	FEV_1 % predicted at baseline	Dose (µg)	Duration	Mean baseline eosinophil count	Mean change in eosinophil count	Risk of bias
Wilson et al. (2006)[68]	8	22	Mild, persistent	69.0	160	4 weeks	6.0%	-1.5%*	Low
Gauvreau et al. (2005)[69]	22	33	Mild	97.7	40 80	5 days	9.0% 5.0%	6.3% 1.6%	Unclear
Erin et al. (2008)[70]	21	26	Persstent	87.0	320 1280	1 weeks	N/A N/A	NS NS	Low
van den Berge et al. (2009)[71]	67	45	Stable	84.4	1600	2 weeks	0.9%	-0.3%*	Unclear
Duong et al. (2008)[72]	12 13	35 40	N/A	100.5 104.5	40/80 160/320	3 weeks	2.5% 3.3%	-0.9% -2.1%*	Unclear
Hoshino et al. (2010)[41]	14	36	Mild, persistent	90.5	200	8 weeks	12.2%	-5.3%*	High

* Statistically Significant ($p < 0.05$); NS – Not significant; ICS – Inhaled corticosteroids; RCT – Randomized controlled trial; FEV1 – Forced expiratory volume in 1 second; µg – Microgram

Table 5. Summary of BD ICS RCTs

Author (year)	Intervention group sample size	Mean Age	Asthma Severity	FEV_1 % predicted at baseline	Dose (µg)	Duration	Mean baseline eosinophil count	Mean change in eosinophil count	Risk of bias
Negro et al. (2003)[73]	10 10	44 47	Mild to moderate	88.1 84.7	400 800	12 weeks	37.6% 44.4%	-3.2% -26.1%*	Unclear
Wang et al. (2005)[74]	19	42	Moderate to severe	52.4	1000	6 weeks	6.6%	-2.56%	High
Lazarus et al. (2007)[75]	44 (non-smoker) 39 (smoker)	29 29	Mild	80.2 78.1	320	8 weeks	N/A N/A	-2.74%* -3.44%*	Low

* Statistically Significant ($p < 0.05$); NS – Not significant; BD – Beclomethasone dipropionate; ICS – Inhaled corticosteroids; RCT – Randomized controlled trial; FEV1 – Forced expiratory volume in 1 second; µg – Microgram

Table 6: Summary of Mometasone ICS RCTs

Author (year)	Intervention group sample size	Mean Age	Asthma Severity	FEV_1 % predicted at baseline	Dose (µg)	Duration	Mean baseline eosinophil count	Mean change in eosinophil count	Risk of bias
Berry et al. (2007)[76]	12	42	N/A	90.3	400	8 weeks	11.0%	-8.7%*	Low
Nelson et al. (2009)[77]	11	38	Mild to moderate	74.0	400	12 weeks	2.5%	-2.0%	Low

* Statistically Significant ($p < 0.05$); NS – Not significant; BD – Beclomethasone dipropionate; ICS – Inhaled corticosteroids; RCT – Randomized controlled trial; FEV1 – Forced expiratory volume in 1 second; µg – Microgram

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Chemotherapy Induced Cardiotoxicity: Facts, Breakthroughs, and Challenges

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ABSTRACT

Chemotherapy involves the use of one or more cytotoxic drugs to kill rapidly dividing malignant cells. One of the most promising fields of chemotherapy is the so-called targeted therapy, where a group of antibodies and small-molecule kinase inhibitors are designed to target key proteins involved in growth and proliferation pathways. Today, targeted therapeutics, such as Imatinib mesylate (Gleevec), have radically transformed the treatment of solid tumors and some blood malignancies. Unfortunately, emerging chemotherapy-associated cardiotoxicity poses unexpected challenges that may limit effective use of these novel drugs. Drug-induced cardiotoxicity is associated with cardiac cell death and cardiac dysfunction, which can lead to life threatening heart failure. The mechanisms underlying this cardiotoxicity remain poorly understood. In this review we discuss the cardiotoxicity of some of the major anticancer chemotherapy drugs, and summarize recent insights into the mechanisms implicated in cardiac cell death and survival.

RÉSUMÉ

La chimiothérapie comprend l'utilisation d'une ou plusieurs drogues cytotoxiques pour tuer les cellules malignes en division rapide. L'un des domaines les plus prometteurs de chimiothérapie est la soi-disant thérapie ciblée, où un groupe d'anticorps et d'inhibiteurs de kinases à petites molécules sont conçus pour cibler des protéines clés impliquées dans les voies de croissance et de prolifération. Actuellement, les agents thérapeutiques ciblés, tels que le mésylate d'imatinib (Gleevec), ont radicalement transformé le traitement des tumeurs solides et des tumeurs malignes du sang. Toutefois, la cardiotoxicité associée à la chimiothérapie pose des défis inattendus qui peuvent limiter l'utilisation efficace de ces nouveaux médicaments. La cardiotoxicité induite par la chimiothérapie est associée à la mort des cellules cardiaques et à la défaillance cardiaque, pouvant conduire à une insuffisance cardiaque mortelle. Les mécanismes sous-jacents de cette cardiotoxicité restent mal compris. Dans cette revue, nous discutons de la cardiotoxicité de certains des principaux médicaments de chimiothérapie anticancéreuse, et résumons les dernières connaissances sur les mécanismes impliqués dans la mort et la survie des cellules cardiaques.

THE CANCER AND ANTICANCER TREATMENTS

Cancer is a malignant growth caused by the uncontrolled proliferation of abnormal cells. Cancerous cells often have genomic alterations at multiple sites producing mutations that, among others, activate oncogenes and repress tumor suppressor genes. Presently, more than a hundred different types of tumors targeting almost all body organs have been described [1,2]. Extensive research into tumor etiologies and cancer progression has resulted in a plethora of anticancer drugs and regimens with varying efficiency at eradicating the disease. At present, cancer therapies can involve surgery, chemotherapy, radiation therapy, and cellular therapy or a combination thereof [3]. This review focuses on chemotherapy and the associated cardiac toxicity often seen in cancer survivors.

Chemotherapy involves a group of cytotoxic drugs that kill rapidly dividing cells by interfering with cell division and DNA synthesis. The subsequent side effect of this approach is that chemotherapy also harms healthy, rapidly dividing cells, such as those lining the gut and forming the hair follicle. Chemotherapy, which is performed to either cure or control cancers, can be used alone or combined with radiation therapy or surgery [3]. A promising field of chemotherapy is the so-called 'targeted therapy', where antibodies or small-molecule inhibitors are designed to target key pro-tumorigenic growth inducing cell surface receptors and/or components of their intracellular signaling pathways such as protein tyrosine kinases. Currently, more than 10 FDA-approved agents exist, with many more awaiting approval, offering hope to patients with cancers that are unresponsive to other treatment modalities. Interestingly, the high mutation rates affecting pro-

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tein kinases in cancers, and their subsequent cancer-driving roles has triggered the search for kinase-specific inhibitory molecules. Today, targeted therapeutics such as Imatinib mesylate (Gleevec), a small molecule targeting the BCR-ABL fusion protein kinase that causes chronic myelogenous leukemia (CML), have drastically transformed the treatment of this malignancy [4,5]. Other pathways, such as the Phospho-Inositol 3 Kinase (PI3K) pathway are also altered in cancer due to mutations or amplifications of several key components, thus making them attractive targets to drug development. Not surprisingly, the pharmaceutical industry is pursuing agents that can inhibit either receptor tyrosine kinases upstream of, or pro-growth kinases associated with the PI3K pathway. There are several agents already in clinical trials, such as the multikinase inhibitor Lenvatinib and the splenic tyrosine kinase inhibitor Fostamatinib [4]. Another aspect of cancer is the dysregulation of cell cycle regulators. Therefore, targeting these factors is currently a major focus in cancer research. In fact, numerous cyclin-D kinases (CDKs) inhibitors, which target these pro-proliferation kinases, are in development with many in clinical trials [3,4,5].

CARDIOTOXICITY OF CHEMOTHERAPEUTIC AGENTS

Chemotherapy-induced cardiotoxicity is a serious clinical problem faced by both cardiologists and oncologists (Table 1). Contractile heart cells, known as cardiomyocytes, are prone to short-term or permanent injury upon exposure to toxic agents such as recreational drugs and therapeutic agents. Unlike most other cells, postnatal cardiomyocytes have limited regenerative capacity. Thus, their loss can cause cardiac dysfunction, which in turn can lead to heart failure, a disease with worse prognosis than some cancers [6]. The realization that chemotherapy might worsen an underlying cardiac problem or create a new one did not become a concern for cardiologists and oncologists until the seventies. The cardiac toxicity of anthracyclines, a class of bacterial antibiotics widely used in chemotherapy, was the first to be described [4-6]. This consequently spurred awareness and extensive research into basic and clinical aspects of chemotherapy associated cardiotoxicity. Although much of the literature focuses on causes and mechanisms implicated in anthracycline-induced cardiomyopathy, other types of chemotherapy-related cardiac toxicity are also common. For example, Cytarabine, an antimetabolic agent, can negatively affect the cardiac vasculature and the pericardium resulting in ischemia and changes in blood pressure, as well as an imbalance in liquid equilibrium and pericardial thickening, respectively [7]. Finally, anticancer drugs such as Imatinib and anthracyclines can aggravate or induce cardiac arrhythmias and other cardiac conditions in patients [4,8-10].

In anthracycline-induced cardiac myopathy, left ventricle (LV) systolic dysfunction is dose-dependent and damage is irreversible, eventually leading to heart failure. Anthracyclines and other drugs that cause irreversible cell destruction are known as type I agents [6,8]. In contrast, many novel drugs that also cause cardiomyopathies, like the monoclonal antibody trastuzumab used mostly in breast cancer treatment, or the VEGF receptor antibody Bevacizumab, usually induce reversible cardiac damage and are therefore referred to as type II agents. Type II agent-induced toxicity is not dose dependent and in most cases reversible upon drug withdrawal [8]. The cardiotoxicity of anthracyclines, and various targeted chemotherapeutic drugs will be the focus of the current review.

ANTHRACYCLINES-INDUCED CARDIOTOXICITY

Anthracyclines have been effectively used as anticancer agents over the past fifty years. They are used in the treatment of leukemias, lymphomas, breast cancer, and sarcomas. They induce cell death through mechanisms that involve DNA intercalation, topoisomerase II inhibition, as well as replication and transcription inhibition. At present, the use of anthracyclines is limited due to their negative effects on the heart, often resulting in cardiomyopathy [8].

Doxorubicin (DOX), the most commonly used anthracycline, has been used since the late 1960s. Tumors treated include esophageal and breast carcinomas, osteosarcoma, soft tissue sarcomas, Kaposi's sarcoma, and Hodgkin's and non-Hodgkin's lymphomas [10]. Furthermore, in many breast cancer patients, DOX is used in conjunction with trastuzumab, a monoclonal antibody against the oncogenic human epidermal growth factor receptor 2 (HER-2, ErbB-2) [11]. As mentioned earlier, the use of DOX has been subdued by reports of fatal cardiotoxic events in cancer patients [1,8,9]. Mechanistically, DOX is known to intercalate DNA and inhibit replication, as well as form a complex with iron, increasing free radical production and inducing oxidative damage characterized by membrane disruption and cellular dysfunction [8,9]. Such effects are especially detrimental to cardiomyocytes, which are highly susceptible to oxidative damage. Other mechanisms that contribute to cardiotoxicity include mitochondrial DNA mutations, calcium handling alterations, and dysregulation of important cardiac transcription factors, such as GATA4 [9]. DOX-induced cardiac toxicity is dose-dependent and cellular damage ranging from vacuolation and contractile elements disarray to cell death, is irreversible [6,8].

Latent DOX associated cardiomyopathies usually occur within one month to one year following treatment induction, but can be observed months after the end of treatment. Known risk factors for cardiotoxicity include older age, hypertension, diabetes, previous cardiac disease, and simultaneous treatment with other anticancer drugs [10]. Various strategies have been developed to diminish the risk of cardiac injury, like the use of DOX analogues, liposomal delivery systems, and the co-administration of putative cardioprotective agents. These approaches have had limited success with the most effective being dosage limitation

and alternative drug delivery methods [8]. Treatments of the resulting cardiomyopathy include angiotensin-converting enzyme (ACE) inhibitors, diuretics, beta-blockers, and digoxin. DOX continues to be used in cancer therapy due to its efficacy in the treatment of many tumors [8,10].

Over the past decades, research on DOX associated cardiotoxicity failed to elucidate its underlying mechanism(s). However, most studies agree on the pivotal role played by DOX-induced oxidative stress, given that DOX chemical structure possesses an inherent tendency to generate free radicals and reactive oxygen species (ROS) during its metabolism. Moreover, mitochondrial DNA damage caused by DOX directly or by ROS was found to cause respiratory chain failure and increased ROS production [12]. On the other hand, DOX cardiotoxicity is enhanced by dysregulation of several pathways including calcium handling, the adrenergic system, and inhibition of critical cardiomyocyte-specific gene(s), such as transcription factor GATA-4. GATA-4, a major regulator of heart development and a postnatal myocytes' survival factor, is depleted rapidly in response to DOX treatment [6]. Interestingly, GATA-4 downregulation was associated with concomitant decrease in both antiapoptotic BCL-XL and BCL-2 gene expression, leading to increased apoptotic cell death. Conversely, enhancing GATA-4 activity by the α1 adrenergic agonist phenylephrine or the adenovirus-mediated overexpression of GATA-4, prevented DOX-induced apoptosis in cardiomyocytes mainly via the transcriptional activation of both BCL-XL and BCL-2 [6,13].

Most of the cellular events mentioned above trigger cardiomyocyte death mainly via apoptosis and necrosis, but other cell death forms, like autophagy, might also play an important role [12,13]. DOX-induced oxidative stress and the subsequent effect on cytosolic calcium homeostasis leads to mitochondrial calcium overload, which in turn triggers mitochondrial permeability transition (MPT) [12]. MPT results in loss of membrane potential, swelling, and outer membrane rupture, releasing cytochrome c and initiating the intrinsic apoptosis pathway [12]. Other studies found that cardiomyocyte death in DOX-induced cardiac dysfunction can be explained partly through a Fas-mediated extrinsic apoptosis pathway [14]. Moreover, necrosis or the more recently described programmed necrosis could play a major role in DOX-induced cardiotoxicity. Mechanistically, ATP depletion caused by mitochondrial uncoupling could favor necrotic rather than apoptotic cell death [15]. Finally, DOX was also found to increase autophagic fluxes in cardiomyocytes essentially contributing to its cardiotoxicity. Once again, increased GATA-4, which controls many genes involved in mitochondrial biogenesis and stress response, inhibited DOX-induced autophagy and reduced cell death, reinstating the central role of GATA-4 as a cardioprotective, prosurvival signal in adult cardiomyocytes [6].

MONOCLONAL ANTIBODIES AND ASSOCIATED CARDIOTOXICITY

In the past decade, the use of monoclonal antibodies that can specifically block the action of oncogenic proteins, mostly growth receptors linked to tyrosine kinases, has significantly improved overall survival of patients suffering from certain cancers (Table 1). For example, trastuzumab (Herceptin) and pertuzumab, are monoclonal antibodies used to antagonize and block the oncogenic activity of HER2 (ErbB2). HER2, which is upregulated in 25-30% of breast cancer patients (HER2+), is responsible for the development and progression of several types of aggressive breast cancers. The mutant, constitutively active HER2 receptor activates growth (MAPK) and proliferation (PI3K-AKT) pathways leading to the uncontrolled division of cancer cells. Trastuzumab and pertuzumab can bind the hyperactive HER2 receptor, forcing its internalization and degradation, and eventually causing cancer cell death [16]. These antibodies are thus potent and widely used breast cancer targeted chemotherapeutic agents, and are usually administered in conjunction with DOX for maximum anticancer efficiency and better patient prognosis [17]. The reported percentage of trastuzumab linked cardiotoxic events in patients ranges between 1.7% and 20% [17,18]. The cardiotoxicity associated with anti-HER2 therapy appears to be dose independent and reversible, although there is present controversy regarding the reversible nature of cardiac damage. Mechanistically, ErbB2 blockade can induce cardiomyocyte cell death through the activation of the mitochondrial apoptotic pathway [19]. Previous or concomitant exposure to DOX increases the risk of cardiac events in anti-HER2 treated patients. Some of the suggested mechanisms include the downregulation of several prosurvival pathways (ERK and AKT pathways), increased accumulation of DOX in cardiomyocytes, and impaired angiogenic and myogenic cardiac programs [20].

Other monoclonal antibodies used as chemotherapeutic agents include the anti-angiogenic Bevacizumab, which binds to vascular endothelial growth factor (VEGF) and Ramucirumab, which binds to the type-2 receptor (VEGFR2). These antibodies potently suppress the proangiogenic VEGF/VEGFR pathway and thus limit angiogenesis in tumors. Unfortunately, the inhibition of the VEGF/VEGFR pathway triggers pathologic alterations in the cardiovascular system [21]. Clinically, around 10% of patients receiving bevacizumab or ramucirumab develop hypertension and 2-3% receiving bevacizumab suffer from heart failure [22,23].

KINASE INHIBITORS AND CARDIOTOXICITY

Kinase inhibitors (KIs) are small molecules that mostly compete with ATP for binding to the kinase ATP pocket. The binding of these molecules blocks the phospho-transferase activity

of an oncogenic kinase preventing the phosphorylation of downstream substrates. KIs bind the pocket with a very high affinity at low cellular concentrations (nM to μM), given the abundance of ATP in a cell (mM) [24]. Type I inhibitors, which target the ATP pocket only, are less selective and often lead to off-target effects and potential toxicity. This poor selectivity is addressed in type II inhibitors, like Imatinib mesylate, which usually recognize other regions of the kinase in addition to the ATP pocket. Type II inhibitors are thus more selective and typically more potent because they can bind and inhibit the kinase in both its active and inactive conformations. Finally, type III inhibitors, target kinase-specific non-conserved regions different than the ATP pocket, and therefore, are excellent selective KIs. Unfortunately, type III inhibitors represent a very small percentage of KIs due largely to design-associated challenges. Interestingly, the superior effectiveness of more selective inhibitors over non-selective ones has been challenged in a variety of oncological and inflammatory diseases, given that non-selective KIs can target other kinases that might be essential for disease progression and would typically lead to a better anticancer efficacy [24]. Finally, non-selective KIs can be used in more cancers and may be more appealing for drug development.

The human kenome is composed of 518 kinases, out of which around 90 are tyrosine kinases (TKs) [25]. Tyrosine kinases can be either receptor tyrosine kinases (RTKs) or non-receptor TKs. TKs are usually heavily mutated or amplified in cancers and therefore the development of therapeutic TK inhibitors (TKIs) has exploded recently. Imatinib mesylate (Gleevec, Novartis), was the first TKI to reach market following FDA approval in 2001. Imatinib approval as an anticancer drug paved the way for several tyrosine-kinase-targeted therapies [25]. Imatinib inhibits the tyrosine kinase activity of the BCR-ABL fusion protein resulting from a chromosomal translocation, known as the Philadelphia chromosome. The BCR-ABL fusion protein dimerization phosphorylates the ABL kinase domain leading to its constitutive activation. This constitutively active kinase activates antiapoptotic pathways (RAS-ERK, PI3K-AKT, JAK-STAT), ultimately enhancing cell division and inhibiting DNA repair leading to chronic myelogenous leukemia (CML) [Reviewed in 26]. During the pre-Imatinib era, CML was treated by anthracyclines, interferons, and bone marrow transplantation albeit with variable successes [reviewed in 27]. The discovery of Imatinib revolutionized the treatment of CML patients, with over 70% cytogenic remission and initially reported minimal side effects, which included peripheral edema and dyspnea. In addition to its inhibition of BCR-ABL, Imatinib inhibits the receptor for stem cell factor (c-KIT), usually upregulated in gastrointestinal stromal tumors (GISTs), and platelet derived growth factor receptors (PDGFRs), which play important roles in other cancers including GIST and glioblastoma [24]. Lately, Imatinib use has been extended to the treatment of more than 10 solid cancers including gastrointestinal stromal tumors and prostate cancer [Reviewed in 26].

Numerous reports on the effect of Imatinib therapy on the development of congestive heart failure (CHF) emerged recently [28-30]. These studies have been highly controversial given the results of IRIS (International Randomized Study of Interferon versus STI571, Imatinib), where the overall incidence of CHF was about 1% in both the imatinib and the interferon arms [31-33]. The discrepancy could be attributed to the lack of accurate and extensive cardiac function monitoring in most cancer clinical trials, and/or to variables that can affect cardiovascular parameters like age, sex, or obesity. When tested *in vitro* in cultured cardiomyocytes and *in vivo* in mice, Imatinib was found to induce cell death associated with early apoptotic features, and to lead to compromised cardiac function, proving that it has the potential to cause CHF. Our lab as well as others found that imatinib-induced cardiomyocyte death was triggered or at least associated with a dysregulated mitochondrial function [26,34], an anomaly aggravated in aging hearts [35].

Mechanistically, Imatinib-induced cardiotoxicity was suggested to be partly due to its direct inhibition of c-ABL in cardiomyocytes. Furthermore, the endoplasmic reticulum stress response was found to be activated in treated cardiac myocytes [34], a situation known to ultimately provoke cell death. Although the pathways implicated in Imatinib-induced cardiac toxicity are still not fully understood, we recently reported that the upregulation of Bcl-2, an antiapoptotic protein, protects against imatinib cardiotoxicity. Remarkably, we also found that this cardiotoxicity is age-dependent and more evident in old mice. Our results provided new insights into the mechanism of Imatinib negative effects on the heart and offered a possible explanation for the current controversy regarding imatinib-induced cardiotoxicity in cancer patients [26]. Interestingly, a new study found that chronic imatinib treatment induces intracellular calcium ion accumulation, pathologic hypertrophy and remodeling, as well as cell death in *ex vivo* and *in vivo* cardiac models [36].

Sunitinib, which is used against renal cell carcinoma and gastro intestinal stromal tumors, and inhibits VEGFRs, PDGFR, and c-kit, was another multitargeted TKI shown to induce cardiotoxicity in cancer patients. Chu et al. reported that 28% of patients receiving the approved dose had 10-15% reductions in the left ventricular ejection fraction (LVEF). They also found that sunitinib induced an increase in mean blood pressure and around 47% of patients developed hypertension [37]. Sunitinib induced mitochondrial injury and apoptosis in cultured rat cardiomyocytes and mice [37]. Finally, in an *in vitro* toxicity assay, sunitinib triggered cardiomyocyte death, metabolic abnormalities, and lipid accumulation. In this same assay, other TKIs were tested and each showed a distinct toxicity profile reflecting the complex and multiple mechanisms implicated in this drug-induced cardiotoxicity [38]. This lack of target specificity and multiple off target inhibition hypothesis is believed to be the major contributor to cardiomyocyte damage and the wide array of cardiovascular anomalies as-

sociated with small molecule kinase inhibitors. Table 1 lists various kinase inhibitors, their target kinases, treated malignancies, and associated cardiovascular events.

DISCUSSION

Cardiac toxicity associated with traditional and targeted chemotherapy has led to the emergence of the new field of cardiac oncology. Lately, many hospitals and health centres have established on-site specialized cardiac oncology units, where oncologists and cardiologists jointly assess individual clinical cases in order to pre-emptively develop carefully monitored treatment protocols. Basic and translational research done on the increasing number of novel antineoplastic drugs has had a huge impact, and scientific breakthroughs continue to shape cancer care protocols in Canada and the rest of the world. Unfortunately, poorly understood roles of many kinases in the heart, as well as the multi-target specificity of small molecule inhibitors are still major limitations facing researchers and health practitioners. On the bright side, with better awareness and development of early biomarkers, such as plasma BNP, cardiotoxicity might become a manageable clinical challenge, but its prevention requires further insight into cardiomyocyte survival, and the development of appropriate drugs targeting these pathways.

CONCLUSION

Understanding cardiac survival pathways would ultimately lead to the development of heart-friendly chemotherapy regimens, or at least cardioprotective designer molecules that would prevent/counterbalance the adverse effects of anticancer drugs on the heart. This important and complex undertaking requires interdisciplinary collaboration among medicinal chemists, biomedical researchers, and clinical scientists from oncology and cardiology. Eradicating chemotherapy induced cardiac toxicity is a formidable challenge to translational medicine.

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Table 1. Targeted chemotherapeutic agents, targets, treated cancers, and associated cardiotoxicity.

Agent	Class	Targets	Cancer	Cardiotoxicity
Trastuzumab	mAb	HER2	HER2+ breast cancer	CHF, Asymptomatic LVEF decline [16,17]
Pertuzumab	mAb	HER2	HER2+ breast cancer	CHF, Asymptomatic LVEF decline [38]
Bevacizumab	mAb	VEGF	RCC, CRC, glioblastoma, NSCLC, breast cancer	Asymptomatic LVEF decline, Hypertension [21,22]
Imatinib	TKI	ABL, c-KIT, PDGFR	CBL, GIST, glioblastoma	CHF, Asymptomatic LVEF decline [24,30,27-29,33]
Sunitinib	TKI	VEGFR, c-KIT, PDGFR	GIST, RCC	CHF, Asymptomatic LVEF decline, Hypertension [36]
Lapatinib	TKI	ErbB1, HER2	HER2+ breast cancer, ovarian cancer, NSCLC	Asymptomatic LVEF decline [40]
Dasatinib	TKI	ABL, c-KIT, PDGR	CML, ALL	QT prolongation, Pericardial effusion [4,41]
Nilotinib	TKI	ABL, c-KIT, PDGFR	CML, ALL	QT prolongation [41]
Sorafenib	TKI	VEGFR, c-KIT	RCC, HCC	CHF, Acute coronary syndrome, Hypertension [41]

mAb, monoclonal antibody; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; RCC, renal cell carcinoma; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; ALL, acute lymphocytic leukemia; HCC, hepatocellular carcinoma.

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Medicine & Humanities At University Of Ottawa's Faculty Of Medicine: Developing A Curriculum For Our Undergraduate Medical Education Program

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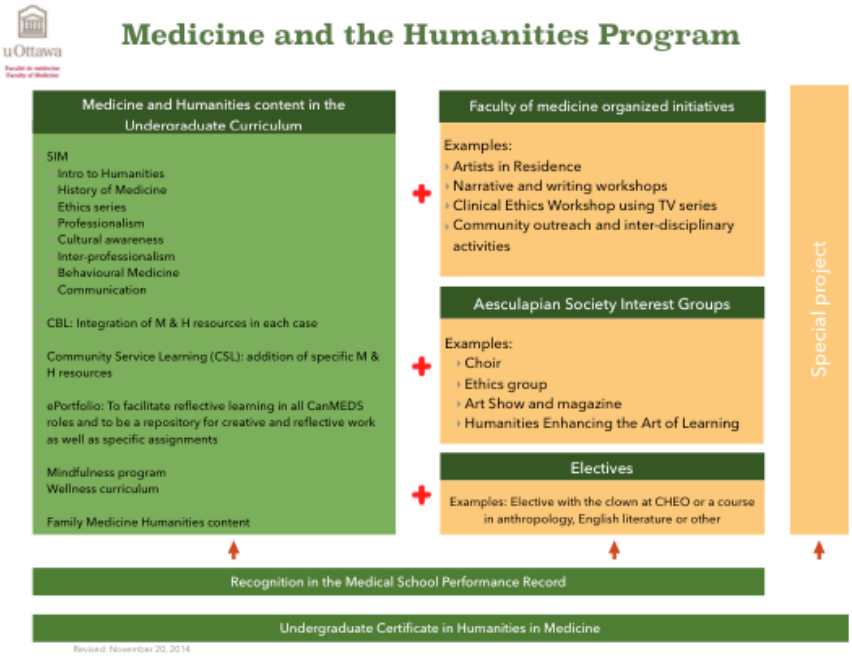
The Medicine & Humanities Program in the undergraduate medical education (UGME) curriculum in the Faculty of Medicine at the University of Ottawa is a new and evolving program. It seeks to enhance our students' education by formally infusing both our French and English streams' curricula with concepts of health, medicine and healing through the humanities, including medical history, philosophy, the arts and literature. There is increasing awareness of the importance of the humanities in the education of health professionals. Often referred to as the 'art of medicine', the humanities contribute to a range of skills necessary for patient interaction, from communication, through cultural sensitivity, to the human values that underpin ethics and professionalism in medicine. In their turn, these values and skills are founded on our cultural traditions, evolving throughout history of medicine. Our current vision of ethics, law, philosophy, human diversity and respect for all patients is a result of this evolution and will change yet again. Medical students need to recognize this, often ephemeral, aspect of medicine.

Our program consists of mandatory curricular components for all students, and extracurricular or elective components for students who wish to pursue medicine, the arts and humanities in more depth. In 2014, a process was developed for students with special interests in this area to obtain either a special recognition for their interest in, and commitment to, the humanities and medicine, or a certificate of excellence in Humanities in Medicine, for which a special pre-approved project is required. All medical students are eligible. Students must submit a request, and document the number of hours they spend on the humanities-based activity. The request is reviewed and adjusted if necessary, and on completion of the activity, members of the Medicine & Humanities committee (or their delegates) award the final number of credits. Below is a diagrammatic representation of the curricular organization.



Keywords: Person; Wellness; Humanities; Medical Education

Why I use Poetry in My Medical Teaching

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When I teach I try to address the people who feel most alienated.

William Carlos Williams was a pediatrician and a poet often thought of as one of the early modernists. His poem "Between Walls" is a famous example of the unsentimental concise sharpness that characterized (some of) modern poetry [1]. It is about looking for a glint of hope or meaning in the sterility of the modern hospital and finding some beauty in the imagery of the broken pieces of a green bottle. This arbitrarily assigned aesthetic- to strewn discarded shards - replaces the romantic subjectivity that the modernists feel that we can't have anymore. Their view is that we have been too overexposed and desensitized to accept conventional symbols.

An important part of medical education is being present with students on a journey of desensitization and trying to provide an anchor for the retention of "humanity", not that I know exactly what that is. I am a pediatric pathologist and my job involves doing autopsies on deceased children. In my training, I felt that to survive I would need to learn to find beauty in the terrible. This was not a modern sentiment. I was never fully modern. I wanted to find salvation in suffering not just discover accidental colors. I saw hints of this in the assignment of names from Greek Mythology in the naming of fetal malformation: Cyclopia, Sirenomelia: the epic battle between mortals and not entirely insurmountable gods.

Modern medicine emphasizes objectivity and the dispassionate gaze. Critics such as Foucault have pointed out that medicine itself is subjective and its beliefs and constructs are predicated more on the prevailing normative culture than objective truths. That has been my experience.

Money is also a big part of it. There is a lot that is commodified, commercialized and corporate. Do we really want more longevity at the price of our spirits and voices? How can there be real meaning when we all sound like mid-level bureaucrats? In this new lingo, we speak litany to litany not heart to heart, so what words do we have to discuss compassion?

Modern poetry is subversive because it puts presence (and then form) over content and thus questions what is valuable, and because it takes authority out of authorship and tells us all to find meaning together. All poetry and perhaps all art (modern or ancient) is subversive because it dwells in possibilities when possibilities have been exiled.

The most widely read Canadian Post-Modern poem is Christian Bok's Eunoia [2]. He chose that title because it is one of the few English words that have all vowels in it. It means "beautiful thinking" and in Greek Philosophy was described as the state of mind one has to be in to make a friend. Artists converge in communities of the disenfranchised and find this state of mind.

I use poetry in my teaching because, in the end, all communities are communities of the disenfranchised and all pedagogy is pedagogy of the misunderstood.

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Keywords: Poetry, Medical Education

Chief Complaint

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ABSTRACT

In the small group sessions of undergraduate medical education at the University of Ottawa, students are presented with a patient's chief complaint in a module that is clear-cut and objective. The cases are often idealistic in a way that can be sometimes statistically rare, but once in a while the patient passes away, leaving students slightly disappointed but undisturbed. Exposure to a patient's triumphs and tribulations may be only a few minutes long, but for the patient and their family, cancer represents a man who is in constant fear of a group of cells killing him, or a father who will never see his grandchildren, or a wife whose absence leaves a sting to everyday life. This poem is an attempt to give a voice to the patient outside the constraints of a presented case, whether it is case-based learning or a presentation in a hospital conference room, and instead to give life to a scenario that is greyer than the black and white typed notes make it out to be.

RÉSUMÉ

Dans les séances en petits groupes, faisant partie de la formation médicale de premier cycle à l'Université d'Ottawa, les étudiants font face à la plainte principale d'un patient dans un module qui est clair et objectif. Les cas sont souvent idéalistes, dans un contexte qui peut parfois être statistiquement rare. De temps en temps, par contre, le patient décède, laissant les étudiants quelque peu déçus. L'exposition aux triomphes et tribulations d'un patient peut ne durer que quelques minutes, mais pour le patient et sa famille, le cancer représente un homme qui vit dans la peur constante qu'un groupe de cellules le tuera, ou un père qui ne verra jamais ses petits-enfants, ou une épouse dont l'absence laisse une douleur à la vie quotidienne. Ce poème tente de donner une voix au patient en dehors des contraintes d'un cas présenté, que ce soit à travers l'apprentissage par cas ou une présentation dans une salle de conférence de l'hôpital, et au lieu, donner vie à un scénario qui est plus gris que font sembler les notes dactylographiées en noir et blanc.

The patient is a 55 year old male, presenting with a 6 month history of progressive shortness of breath, chest pain, dysphonia, and constitutional symptoms which included weight loss and night sweats –

"This last summer was a vague memory
of puzzle pieces that I attempted to assemble together,
because despite the crisp breeze and warm weather,
I felt under a cloud.
A voice gone hoarse and a persistent cough
laid a shroud of obscurity in my mind,
but what kind of heavy cloak weighed me down,
unable to run freely with my son playing football?
Yet with the illusion of being out of shape,
I saw my shape wither away in the mirror,
bones appearing where flesh once was,
a paradox I could not figure out."

His chief complaint at first visit was a two-day history of hemoptysis –

"Aunt from aunt, nephew from nephew,
there were only a few of them who did not notice a change
in the person whose exterior was stagnant for years.
I pushed down the fears about my weight or my pallor,
yet the family reunion turned sour
when my chest roared with bronchial cries of mutiny,
and out came a red badge of courage on my napkin.
Not since Lady Macbeth had someone hated a damned spot so.
I felt I would drown in that spot,
as if the puddle would expand into an ocean,
where a whirlpool of images from the cigarette warning labels
that I'd so stubbornly ignored would pull me in to face my worst
nightmares."

Keywords: Poetry, Medical Education

Investigations showed low hemoglobin, low sodium likely due to the paraneoplastic Syndrome of Inappropriate Antidiuretic Hormone, and a left upper lobe nodule on chest X-ray –
"The physician glowed under the light
of the black and white image of my insides,
and pointed to the cloudy smudge that was killing me.
So there it was, that little puff of death,
the one that slowly managed to take my breath away,
to take my life away before I could say a word of defense.
In the meantime, I felt my sense of permanence in this world
slip out of my fingers,
only for the dread and numbness to linger long enough to replace it."

- consistent with a diagnosis of a lung cancer, where biopsy specified this as squamous cell carcinoma. Risk factors included a 20-pack year history –
"If I could have revisited my younger selves
to pluck every cigarette from their mouths,
I would have done so without shame,
but how am I to blame for being victim to
Man's unwavering lack of acceptance
that he is not but an erasable spot in this world?"

- which, along with the neoplasm, likely contributed to the low scores on pulmonary function tests. Fitness tests, along with CT, showed an inoperable, unresectable mass –
"The only thing that could save me had already passed me by,
but yet the physician did try to offer me a sliver of hope when they –"

- offered a treatment of chemotherapy, which included Cisplatin and Vincristine, as well as radiation –
"Bags filled with alien-named poisons were brought to me
by women who were cloaked in blue gowns,
only to protect themselves from the very liquids
that they were injecting into my veins.
The radiation was the same,
a game of burning laser tag on my chest.
The rest was pills to be taken at home."

The patient experienced the typical side effects, such as nausea and vomiting –
"I could see my wife from the corner of my eye,
her face buried into my son's shoulder as she cried,
while I clasped for dear life the white porcelain,
only to emit projectile acid into the bowl.
I stared at the floating remnants of the dinner she had slaved over, my favourite dish to pick up my mood."

- but despite treatment, the patient's following PET scan revealed metastases to the liver –
"No matter the chemical torture I put myself through,
the devil in my lung managed to spew
into the other vital organs of my body.
I suppose one home was not enough for the vile creature,
who attempted to eat me from the inside out.
And yet again, my life slips from me more and more and more and more…"

Palliative support was given, and the patient signed a DNR document –
"The hospital room has a nice view.
What wasn't a nice view was the one below my chin,
the one of myself hooked up to a tank,
as if I was Jacques Cousteau exploring the sea.
How ironic that I still feel like I'm drowning.
I can see children playing outside in the sunshine,
likely similar to the grandchildren I will never see.
Children, do you not know your fortune?
Play, laugh, love, sing, run, BREATHE while you still can…"

The patient experienced abrupt hematemesis, chest pain, and shortness of breath. Upon CT, hospital-acquired pneumonia was diagnosed and IV antibiotics were given –
"All is a blur,
I cannot stir,
yet the whispers I do hear
from my loved ones are clear -
I am leaving this world loved."

Unfortunately, the pneumonia led to septic shock, which, despite intubation and steroid treatment, resulted in the demise of the patient.

Now onto the next case.

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