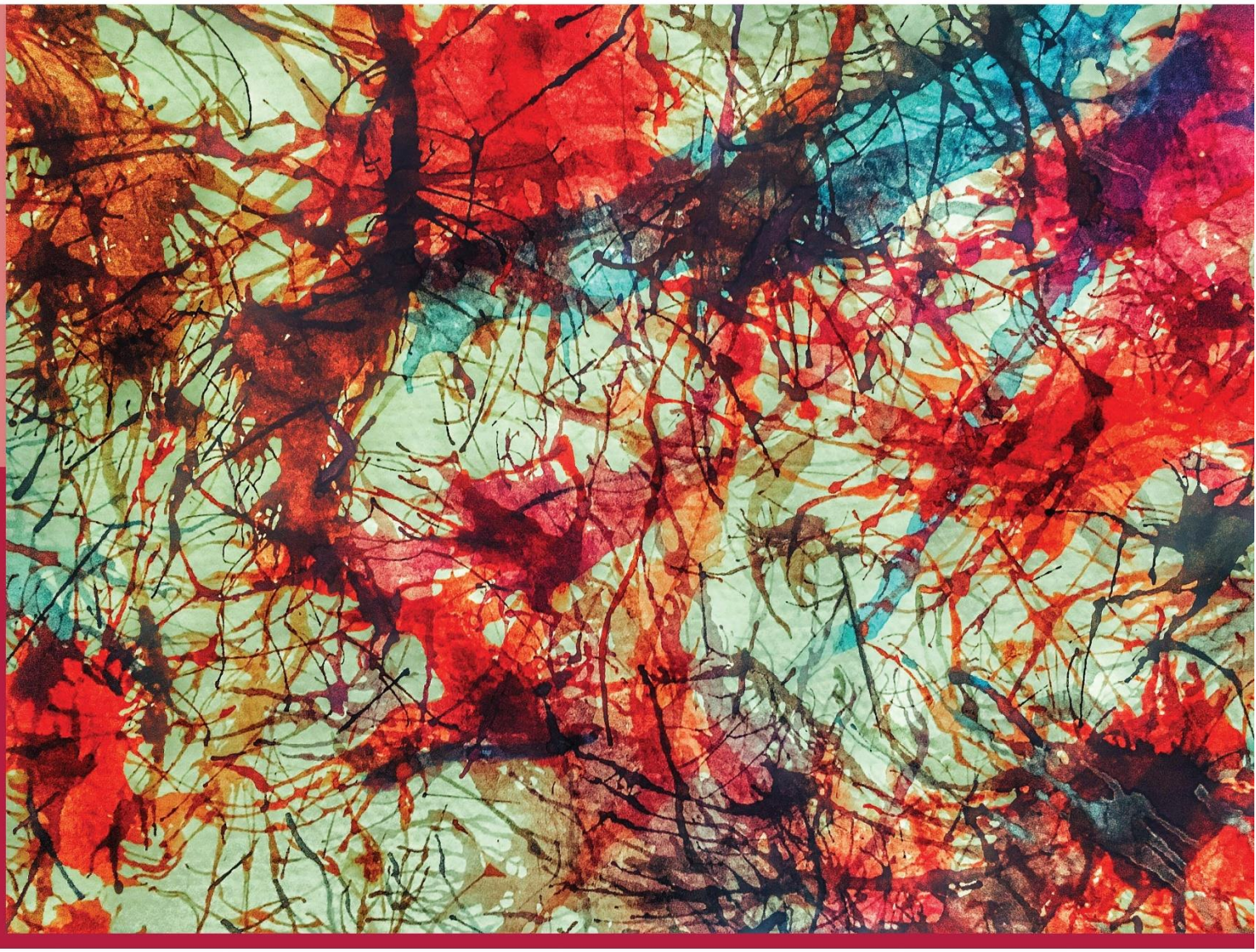
MUMJ

A PEER-REVIEWED, STUDENT-RUN PUBLICATION

McMASTER UNIVERSITY
MEDICAL JOURNAL

VOLUME 16, ISSUE 1 | 2019



McMaster University

The **life** you've been **working** for…

www.bchsys.org

Family Physicians

Live in a community large enough to build a leading-edge facility with colleagues who call you by your first name. A variety of practice options that utilize EMR and function as turn-key operations are available. Situated between Hamilton and London, we are less than an hour drive from each. In fact, Toronto is only an hour away.

As a Family Physician in Brant County, you'll enjoy working in a diverse, under-serviced population of 130,000. Located in the picturesque Grand River Valley, our community offers an unmatched natural playground. With Laurier and Nipissing Universities and top-notch private schools, educational opportunities for you and your family abound. Call today to find out more. You'll be surprised by all that Brantford-Brant has to offer.

For a tour of our community, please call Alice Preston at 519-751-5544 ext. 2354 or e-mail alice.preston@bchsys.org.

Brant Community Healthcare System

McMaster University Medical Journal

Editorial Board 2018-19

TABLE OF CONTENTS

COMMENTARIES

Editorial

McMaster University Medical Journal, Volume 16

Alyson Holland MD, PhD, and Amir Safavi MD, MSc

Editors-in-chief
Michael G. DeGroote School of Medicine, Class of 2019

With our 16th volume we are proud to continue the McMaster University Medical Journal's mandate to showcase work by Canadian medical and graduate students. Our goal is to share advances in medicine, explore the social issues that impact the health of individuals and populations, and provide a space for continuing discourse on ethical and legal issues that are relevant to medicine. Through original research, review articles, and commentaries the papers in this volume demonstrate the breadth of contemporary topics that intersect with medicine and the importance of multi-disciplinarity in medical research.

Through a case study, Campbell, Auer, and Martin explore a unique case of concurrent comorbidities in the form of Kikuchi-Fujimoto Disease and neuropsychiatric lupus in a patient. Similarly, Harris, Rostom, and Moloo discuss the use of single balloon enteroscopy in the treatment of a patient with jejunal varices. Our original research articles range from an intervention to standardize pre-operative clinics in the Niagara region by Brown, Leveille, Paraiso, Nykolaychuk, and Law, to the importance of increasing food knowledge in children to support future health by Lovrics, Plourde, Hendrickson, and Frasier. The role of socioeconomic factors in disease diagnosis and treatment was investigated by Li et al. in breast cancer patients in Hamilton, Ontario, while Endres highlighted the importance of promoting community service to medical students through a new initiative in Ottawa, Ontario.

In a review article, Visva and Oliveria take a detailed look at current understandings of multiple sclerosis while Breton asks us to consider the side effects of atypical antipsychotics. At the same time the commentaries bring our attention to the "big picture" issues in medicine. Levesque deconstructs the discourse surrounding aging and immortality, while Sharma and Rowe bring the focus to antibiotics and resource stewardship in this current climate of burgeoning resistance. Finally, Hariharan and Patel raise questions about the harms of overtreatment in the case of tonsillectomy.

We are exceptionally grateful to the executive editors, submission editors, and reviewers who have generously contributed their time to produce this volume. Journals require a great deal of hard work and without the support of our volunteer staff creating the MUMJ would not be possible. We thank the authors for the opportunity to share their work – through their articles we

are presented with new and emerging ideas, while simultaneously being reminded to ask questions and challenge our understandings; in other words, to know what we don't know. Thank you to our readers, without you there would be no journal. We hope you enjoy reading the 2019 volume of MUMJ.

Original Research Article

A case of concurrent Kikuchi-Fujimoto Disease and neuropsychiatric lupus in a patient with rheumatoid arthritis and systemic lupus erythematosus overlap syndrome

Tessa Campbell MD, PhD[a], Iwona Auer MD, FRCPC[b] and Liam Martin MB, MRCPI, FRCPC[a]

[a]Division of Rheumatology, Department of Medicine, University of Calgary

[b]Department of Pathology & Laboratory Medicine, University of Calgary

Abstract

Kikuchi-Fujimoto disease is a rare, self-limited, histiocytic necrotizing lymphadenitis characterized by cervical lymphadenopathy and fever. An association has been made between the presence of this disease and systemic lupus erythematosus. We describe a unique case of a 31 year old female with a previous diagnosis of rheumatoid arthritis and lupus overlap syndrome who presented with severe headache and subsequently developed altered level of consciousness and seizures. She underwent an extensive assessment which included investigations for an infectious cause, numerous imaging studies, a lymph node biopsy, a bone marrow biopsy, and a brain biopsy resulting in a final diagnosis of concurrent Kikuchi-Fujimoto disease and lupus-associated encephalitis. In these overlap patients, neurological involvement is usually mild. In contrast, our patient presented with severe neuropsychiatric involvement eventually requiring ICU admission. This case highlights the difficulty of diagnosing and managing neuropsychiatric lupus in these complex overlap patients. Early recognition is important to avoid unnecessary and potentially harmful interventions and treatments.

Keywords: Kikuchi-Fujimoto, Lupus, Rhupus

*Corresponding Author: tessa.campbell@ahs.ca

Introduction

First described in 1972, Kikuchi-Fujimoto disease (KFD) is a rare, self-limiting condition of histiocytic necrotizing lymphadenitis characterized by fever, cervical lymphadenopathy and elevated inflammatory markers.[1,2] The etiology of KFD is still unknown, though environmental factors such as infectious exposure have been proposed.[2] KFD has also been reported to be associated with systemic lupus erythematosus (SLE).[1]

Like KFD, the occurrence of overlapping clinical and immunological features of both rheumatoid arthritis and SLE, first described as "rhupus" by Schur in 1971, is a rare clinical condition.[3,4] Overall, rhupus has a prevalence of 0.09% and constitutes 0.01-2% of all systemic rheumatic disease.[5,6] In these overlap patients, erosive features of rheumatoid arthritis are more pronounced, while systemic lupus features, including neurological involvement, are usually mild.[6,7]

In contrast, we describe a case of a rhupus patient with severe neuropsychiatric involvement requiring ICU admission. After an exhaustive work up, the patient was diagnosed with concurrent Kikuchi-Fujimoto disease and lupus-associated encephalitis. She demonstrated remarkable recovery after treatment with corticosteroids and mycophenolate mofetil.

Case report

Our patient is a 31-year old female with a history of SLE and rheumatoid arthritis overlap syndrome, interstitial lung disease, pulmonary hypertension, treated latent tuberculosis, shingles and migraines who presented with headaches and an evolving clinical course resulting in a prolonged and complicated hospital stay. The following services were involved in her care: Internal Medicine, Intensive Care, Respirology, Infectious Disease, Dermatology, Gastroenterology, Pathology, Hematology, Neurology, Plastic Surgery, and Rheumatology.

She first presented to a local Emergency Department with a three week history of severe headache and was treated empirically with ceftriaxone and vancomycin for possible aseptic meningitis. She re-presented approximately two weeks later with an altered level of consciousness and subsequently developed seizures. Numerous investigations were performed to determine the etiology of this change in clinical status. Additionally, the patient was started on ceftriaxone, vancomycin and acyclovir. A lumbar puncture revealed high protein and lymphocytic pleocytosis. An MRI brain indicated diffuse leptomeningeal and pachymeningeal enhancement. Additionally, a CT chest included as part of the ongoing infectious work up demonstrated diffuse axillary lymphadenopathy. An excisional lymph node biopsy was performed to rule out lymphoma. A bone marrow biopsy was also performed, demonstrating moderate normocytic anemia. Investigations for an infectious cause were negative (blood cultures, fungal cultures, human immunodeficiency virus, herpes simplex virus, mononucleosis, varicella zoster virus, cytomegalovirus, polyomavirus, enterovirus, parechovirus, West Nile virus, rickettsiae, methicillin-resistant staphylococcus aureus, clostridium difficile, vancomycin resistant enterococcus, cryptococcus, urine culture, Hepatitis A/B/C, parvovirus, human T-cell

lymphotropic virus I/II, bartonella, histoplasma, coccidioides, blastomyces, and toxoplasma). She was noted to have low levels of complement C3 and C4. Due to the presence of high numbers of lymphocytes in her cerebrospinal fluid and her immunocompromised state on a background of prior treated latent tuberculosis, she was started on empiric anti-tubercular treatment (isoniazid, rifampin, pyrazinamide, levofloxacin). Her vancomycin was continued.

She developed new onset expressive aphasia one month after admission. A CT cerebral angiogram indicated new hypoattenuation of her right occipital lobe. She received three doses of pulsed intravenous solumedrol and was then treated with high dose oral prednisone. Her level of consciousness significantly improved. Incidentally, she was also noted to have upper extremity cephalic/basilic vein thrombosis and was started on dalteparin. A prior anti-phospholipid antibody work up was negative.

As her steroid dose was tapered, the patient's status deteriorated and she required intubation and admission to the Intensive Care Unit (ICU). Her lymph node biopsy returned as necrotizing lymphadenitis suggestive of Kikuchi-Fujimoto disease with no evidence of lymphoproliferative disorder (Figure 1). However, as her diagnosis was still unclear, a brain biopsy of the dura and right frontal area was performed. This indicated necrotizing leptomeningitis with no evidence of vasculitis, microglial nodules, perivascular cuffing or microbial organisms. A new MRI brain showed regression of the leptomeningeal enhancement. Cerebrospinal fluid flow cytometry was negative for malignant cells. Additionally, an electroencephalogram indicated abnormal and slow movements with no epileptiform activity. However, new black discoloration of the left hand 2nd and 3rd distal digits was noted, and Plastic Surgery was consulted. Skin biopsy results indicated epidermal necrosis likely secondary to the pressor support therapy she received while in the ICU.

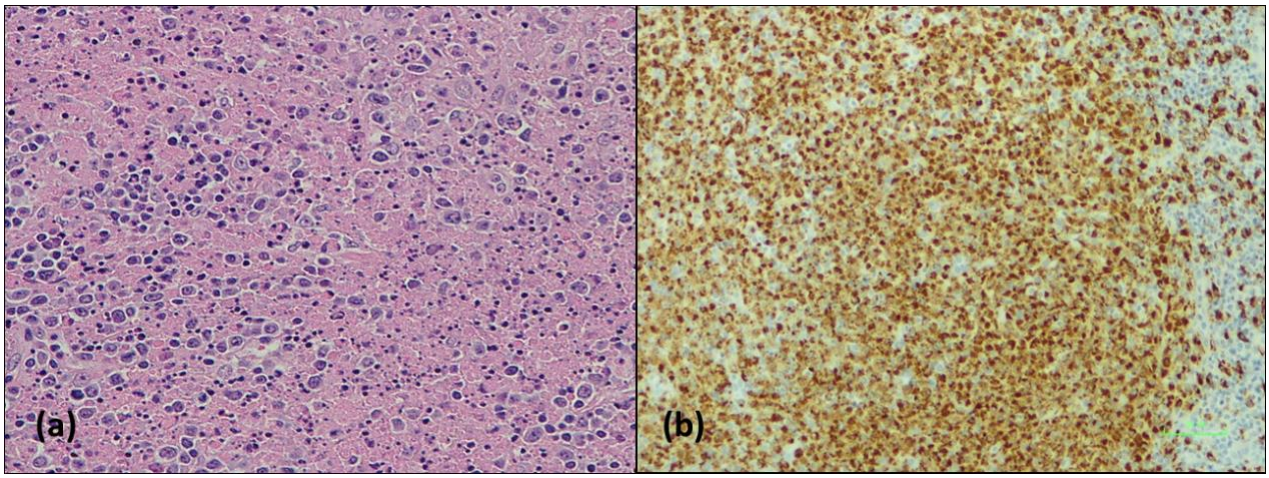


Figure 1. Right axilla lymph node biopsy highlighting (a) a necrotizing area featuring eosinophilic fibrinoid deposits with nuclear fragments, karyorrhexis, apoptotic cells, and paler staining histiocytes suggestive of Kikuchi-Fujimoto disease (Hematoxylin and eosin staining, 40X magnification) and (b) CD68/MPO positive histiocytes (immunohistochemical staining, 40X magnification).

Two weeks later, the patient began to experience cytopenias, fevers, and elevated liver enzymes attributed to the ongoing tuberculosis treatment. She also displayed diffuse erythema thought to be due to vancomycin sensitivity. Moreover, as part of an ongoing infectious work up, the patient was tested for possible additional sexually transmitted infections and was found to be positive for chlamydia. She was treated for chlamydia with azithromycin and started on meropenem for febrile neutropenia. Her tuberculosis medications and vancomycin were discontinued.

She was extubated one week later. Her cognitive status slowly improved. Following a comprehensive review of her clinical scenario at Rheumatology Rounds, a diagnosis of lupus-associated encephalitis was made and the patient was started on mycophenolate mofetil. Her clinical status continued to improve and repeat blood tests for complement levels were normal. Her anti-dsDNA antibodies, anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies, and N-methyl-D-aspartate were negative. The lymph node biopsy results were revisited and the presence of Kikuchi-Fujimoto disease was confirmed. She was discharged from the hospital with follow up arranged with Respirology, Plastic Surgery, and Rheumatology.

Discussion

The diagnosis and management of central nervous system involvement in SLE remains challenging due to the wide range of symptoms and lack of diagnostic criteria.[8] This difficulty is magnified in complex patients with overlap syndromes such as rhupus. Our patient underwent an extensive work up for infectious, neoplastic, and autoimmune causes of her altered level of consciousness, seizures and aphasia. Ultimately, she was diagnosed with an exacerbation of her systemic lupus based upon the presence of hypocomplementemia and non-infectious encephalitis, with concurrent biopsy-proven Kikuchi-Fujimoto disease. She was successfully treated with corticosteroids and mycophenolate mofetil.

In rhupus patients, neurological involvement is usually mild. In contrast, our patient presented with severe neuropsychiatric involvement requiring a lengthy hospital stay with admission to the ICU. This case highlights the need for better guidelines for diagnosing and managing neuropsychiatric lupus in these complex overlap patients. Early recognition is important to minimize unnecessary and potentially harmful interventions and treatments. [2,7]

Acknowledgements

We would like to thank the case study patient for granting permission for publication.

Declarations

Consent for publication

Consent for case publication was obtained from the patient prior to submission.

Competing interests/source of funding

None to declare.

References

1. Dumas G, Prendki V, Haroche J, Amoura Z, Cacoub P, Galicier L, et al. Kikuchi-Fujimoto Disease: Retrospective study of 91 cases and review of the literature. Medicine 2014; 93(24):372-382.
2. Dalugama C, Gawarammana IB. Fever with lymphadenopathy – Kikuchi Fujimoto disease, a great masquerader: a case report. J Med Case Rep 2017; 11:349-352.
3. Schur PH. Systemic lupus erythematosus. In: Beeson PB, McDermott W (eds). Cecil-Loeb Textbook of Medicine. 13th ed. Philadelphia: WB Saunders. 1971; 821.
4. Sarkar S, Saha K. Bilateral acute lupus pneumonitis in a case of rhupus syndrome. Lung India 2012; 29:280-282.
5. Shovman O, Langevitz P, Shoenfeld Y. Rhupus; unusual presentations. Clin Rheumatol 2015; 34(12):2041-2046.
6. Wang JG, Tang HH, Tan CY, Liu Y, Lin H, Chen YT. Diffuse lupus encephalopathy in a case of rhupus syndrome. Rheumatol Int 2010; 30(7):961-3.
7. Liu T, Li G, Mu R, Ye H, Li W, Li Z. Clinical and laboratory profiles of rhupus syndrome in a Chinese population: a single-centre study of 51 patients. Lupus 2014; 23(9):958-963.
8. Goswami D, Chatterjee S, Ahmad B, Das S. Two case reports indicating the dilemma in diagnosing Lupus Cerebritis. J Family Med Prim Care 2013; 2(1):111–114.

Original Research Article

An interactive after-school nutrition and culinary education program for primary school students: The evaluation and efficacy of changing food-related knowledge, attitudes and behaviour

Olivia Lovrics[a], Hugues Plourde[b], Mary Hendrickson[b], and Beccah Frasier[c]

[a] Department of Medicine, Master University, Hamilton, Canada

[b]School of Human Nutrition, McGill University, Montreal, QC, Canada

[c]NDG Food Depot and Boîte à Lunch, Montreal, QC, Canada

Abstract

Objective: To evaluate the efficacy of a 10-week afterschool nutrition and culinary education program in changing the culinary and nutritional behaviour, attitudes and knowledge of its 9-11-year-old participants, as assessed by parents and children.

Methods: Retrospective matched-pairs analysis of secondary pre-post survey data collected by Boîte à Lunch (BàL). Children (n=165-197; grades 4 and 5) and parents (n=53-57) who signed-up for the BàL workshops. The program was comprised of ten-week (2 hours/week) bilingual (French and English) themed sessions led by trained educators with focus on culinary skill development, nutrition education and hands-on cooking. Secondary objectives include: team-work, kitchen hygiene, compost, understanding of food systems. Workshops were held in community centres and schools in Montreal, Canada. Changes were analyzed using the expanded exact McNemar-Bowker test with a Bonferroni-adjusted significance level of 0.001631.

Results: Culinary skill and knowledge improved based on all 23 measures (all $p<0.001631$). Of the six measures assessed for change in attitude, three were significantly improved. Of the two items used to asses a change of behaviour, one was significantly improved. 2 stand-alone post-workshop questions suggest a positive trend for improvements in each.

Conclusion: Knowledge and culinary skill of youth can be improved through nutrition education and hands-on cooking. Culinary and nutritional attitudes and behaviours may be improved; further research is needed.

Keywords: Nutrition education, culinary education, culinary attitudes
Corresponding author: olivia.lovrics@medportal.ca

Introduction

Globally, the average individual is cooking at home less frequently and is less skilled in the kitchen; concurrently, obesity rates are rising[1-6]. Children are especially vulnerable to these changes, as they lack the autonomy to choose, purchase, and prepare their own meals[7]. Consequently, children are frequently not taught basic nutrition or culinary skills in the home and increasingly rely on take-away foods for sustenance[1,4-6]. This is of concern for numerous reasons, including the finding that culinary skill and nutrition knowledge have both been shown to impact diet quality, and that children who are involved in meal preparation consume healthier diets[1,2,7]. Nutritional knowledge and culinary skill increase the variety of foods available to individuals for cooking and consumption, and enables individuals to prepare meals that contain less salt, sugar, and fat than common take-away meals[8]. Additionally, nutrition and food-related behaviours created in childhood are often maintained throughout life and may predict diet quality and health outcomes in adults[1-3,9].

Nutrition and culinary education programs (NCEPs) are used globally to address deficient culinary skills and nutrition knowledge[3,7,8]. Programs designed for children show mostly positive results relating to children's culinary self-efficacy, diet quality, and nutrition knowledge[4,8,10-12]. However, many of these programs lack rigorous and validated evaluations of efficacy due to budgetary constraints, difficulties in assessing outcomes in children and not including parental feedback and/or the lack of long-term follow-up[7,13]. Evaluation is an integral component of well-designed programs, yet there is currently no gold standard for the evaluation of NCEPs in children[2].

Boîte à Lunch (BàL) is an NCEP that has been running for 30 semesters in Montréal, Canada. Throughout these semesters, over 1500 children in grades 4 and 5 from food-insecure homes have participated in the free 10-week program. Each BàL workshop is led by at least 2 trained educators and additional volunteers who engage up to 18 children in weekly lessons which include food preparation, nutrition education, and tasting opportunities. Children participate in nutrition-themed games and hands-on cooking activities where they prepare two healthy recipes to bring home for dinner or for lunch the next school day. Sessions also include lessons on composting, gardening and/or kitchen hygiene. Parents are invited to participate in the program through regular volunteering, participation in the year-end party, consumption of weekly newsletters, and by continuing to promote the program's lessons by preparing BàL recipes at home with their child. This program is unique to others in the literature due to the bilingual nature of the program, the variety of topics taught (i.e. nutrition, culinary skill, food familiarization, composting, gardening, hygiene), and the involvement of parents in the programming.

This research aims to answer three primary questions regarding the skills and knowledge acquired by the children, and to determine if a change in attitudes and behaviours results from program participation. Specifically: Does participation in BàL lead to changes in:

1. The cooking-skillset of the child (change in culinary skill and knowledge)?

2. Fruit and vegetable consumption/willingness to try new foods (change in attitude)?
3. The level of home involvement in food preparation (change in behaviour)?

Based on published evaluations of similar programs, it was hypothesized that BàL workshops would produce positive results for all aforementioned objectives[5,6,8,10-12,14]. Due to differences in program structure between BàL and other programs in the literature (i.e. duration of program, methods of assessment, bilingual lessons etc.), the results of this study are novel addition to the literature. Additionally, the collection of both child and parental feedback corroborates perceived changes due to the program; this is a strength of the study as it is not often included in NCEP evaluations.

Methods

This pre-post, no control, evaluation-design study was conducted using secondary parent and child questionnaire data provided by BàL. Children voluntarily signed-up for the NCEP with recruitment taking place via advertisements placed in municipal recreation centres, grocery stores, and online. The workshops were held in schools or municipal centres in Montreal. Each semester, there were between 6 and 8 classes running in parallel, each with a maximum of 18 students. Each child came to one predetermined 2-hour workshop afterschool, each week, for 10 weeks (1 semester). Workshops were run by at least 2 trained nutrition educators, dietitians, animators, and volunteers. Sessions began with a spotlight on a specific food (e.g.: bok choy), then the recipes were read by the children in both French and English, the recipes were prepared, followed by an additional lesson (e.g.: nutrition, body systems, composting, kitchen hygiene etc.), tasting, and cleaning. The research team was not involved in the production of the workshops. All parents and children signed consent/assent to answering both pre- and post-workshop questionnaires as a part of regular programming. Parent and child questionnaires were completed as either a hard copy or online, at or before the beginning of the first workshop, and within 2-3 weeks of the last. Data were collected and entered into Excel by members of the BàL team immediately after collection; analysis occurred during the study period, up to 1 year following the completion of the semester. No control group was used in this study.

Questionnaires were designed by the BàL team (nutrition educators, community chefs, trained animators, and nutrition coordinators). The researchers' only role was in data analysis. The questionnaires were initially developed by the BàL team to determine if the program was meeting the objectives set forth by stakeholders and members; item formulation was the sole product of informal discussion between involved parties. The questionnaires evolved over time in response to informal feedback and the addition of new program objectives; data analyzed in this study was collected between Winter 2017 and Winter 2018 (Three 10-week semesters). Complete questionnaire responses were removed from analysis if either the pre-workshop or post-workshop questionnaire was missing. If a response was missing on an otherwise complete questionnaire, the remaining survey responses were included while the response paired to the missing data was not. Missing data resulted in variable number of responses per item: between 156 and 198 child responses, and between 56-57 blinded parent pre-post responses.

To determine if a change in child knowledge, attitudes, and behaviour occurred due to participation in the workshop, a matched-pairs analysis was used wherein children and parents acted as their own controls. Each individual's pre-workshop responses were compared with their own post-workshop responses. For analysis, the three semesters were pooled. Institutional review board approval was provided by BLINDED Research Ethics Board.

Questionnaires

Unique pre-workshop and post-workshop questionnaires were administered to parents and participants. Questionnaires were designed over time by the BàL team to address questions asked by program stakeholders. Questions were the unique work of the BàL team and were not scientifically piloted, though informal feedback allowed for the evolution and improvement of the questionnaires Questions were edited to optimize comprehension and added or removed to ensure assessment of all pertinent objectives. The questionnaires addressed many different topics: nutrition habits, food-related attitudes and behaviours, culinary knowledge, and parental engagement.

The questionnaire administered to the children, titled *Skills Checklist* (*SC*) addressed the three main objectives using a 3-point Likert scale: 1 = no/disagree, 2 = a little/neutral, 3 = yes/agree. A higher score was more positive in each question. The *Parental Survey* (*PS*) included questions relating to perceived effects of the workshops, potential behavioural or attitude changes in the child, and home cooking frequency and involvement. A 5-point Likert scale was used ("no, not at all" to "yes, very much") that was merged to a 3-point Likert scale due to low statistical counts. The three objectives were assessed using these questionnaires responses.

The responses to these questionnaires were given to the researchers by the BàL team deidentified. Neither workshop locations nor names of parents/children were given to the researchers.

Domains

Culinary Knowledge

Measures assessing culinary skills included 21 items on the *SC*, and 2 items on the *PS* (see Table 1 in results for list of items). Children ranked their culinary skills for a variety of techniques, such as reading recipes and measuring ingredients. Parents ranked child culinary efficacy and mastery of basic culinary skills, such as using measuring tools, cutting with a knife, and using a food processor.

Attitude

The overall attitudes measure used responses from six questions; 3 from the *SC*, and 3 from the *PS* (Table 2). Children ranked their willingness to try new foods and perceived frequency of

fruits and vegetable consumption, while parents answered similar questions about the child's consumption habits. One post-workshop-only question was included in the parental questionnaire: "Has your child tried new foods at home since the beginning of the BàL workshops?". This question was a yes or no question that was included in the analysis as the percentage of answers indicating "yes".

Behaviour

A change in behaviour was represented in the questionnaires as a change in child involvement in food preparation at home (Table 3). This measure used two similar items on the child and parent questionnaires asking about perceived frequency of cooking together at home. Additionally, one post-workshop-only question on the *PS* asked: "Since the beginning of BàL, my child and I cook more together". This question, using the collapsed 3-point Likert scale, was analyzed as the percent who described themselves in each category.

Statistical analysis

Data were analyzed using SPSS version 24. Cross tabulations were computed to determine the direction of possible changes for each question in the pre- and post-questionnaires. The expanded exact McNemar-Bowker test was used for each item to compare pre-post responses. Statistical significance was set at $\alpha = 0.05$; because multiple tests were conducted on the same dataset, the Bonferroni correction was used to reduce the probability that the results were due to chance[15]. For the three objectives, a total of 31 metrics were used therefore the Bonferroni adjusted significance level becomes $\alpha = 0.05/31 = 0.001613$. This method allows for direct comparisons of the individual changes experienced, as opposed to comparisons of group level responses. Comparing frequency of participants who agreed or disagreed with questions would not reflect the individual changes and therefore was not used.

The impact of the workshop on the three overall research questions was determined by summation of the number of questions included in each objective that yielded a significant change, compared to the total number of measures that constitute each objective, similar to as was done in a study by Cunningham-Sabo and Lohse[11]. If more than half of the questions demonstrated a statistically significant change, that objective was said to have undergone a statistically significant change.

Results

For all questions, the direction of score change between pre-post questionnaire indicates a positive change, with the exception of "My child is open to trying new foods" (*PS*) which was not statistically significant. Results below are split based on overall outcome.

Table 1. Quantitative results for objective one (change in knowledge from pre-workshop to post-workshop). All 23 measures showing statistically significant improvement in culinary knowledge and skill over the course of the workshops.

Metric	n (matched)	Mean Pre-Workshop Response	Mean Post-Workshop Response	p-value
I know how to read a recipe (SC)	165	2.65	2.89	P < 0.001
I know how to follow a recipe (SC)	173	2.57	2.85	P < 0.001
I know how to prepare a recipe without help (SC)	168	2.03	2.51	P < 0.001
I know how to measure with a teaspoon (SC)	171	2.24	2.75	P < 0.001
I know how to measure with a tablespoon (SC)	170	2.21	2.78	P < 0.001
I know how to measure with a cup measure (SC)	174	2.20	2.78	P < 0.001
I know how to measure with a thermometer (SC)	171	1.65	2.09	P < 0.001
I know how to use a peeler (SC)	176	2.35	2.85	P < 0.001
I know how to use a grater (SC)	176	2.65	2.95	P < 0.001
I know how to use a knife (SC)	175	2.67	2.94	P < 0.001
I know how to use a juicer (SC)	175	2.36	2.81	P < 0.001
I know how to use a whisk (SC)	175	2.70	2.88	P = 0.001
I know how to use a microwave oven (SC)	172	2.47	2.74	P < 0.001
I know how to use a food processor (SC)	176	1.97	2.55	P < 0.001
I know how to use the oven (SC)	169	2.34	2.80	P < 0.001
I know how to crack an egg (SC)	176	2.10	2.59	P < 0.001
I know how to dice (SC)	176	2.67	2.91	P < 0.001
I know how to cut in slices (SC)	196	2.41	2.89	P < 0.001
I know how to use a rolling pin (SC)	195	2.51	2.92	P < 0.001
I know how to fill a muffin tin (SC)	197	2.44	2.85	P < 0.001
I know how to cook (SC)	178	2.42	2.83	P < 0.001
My child knows how to cook (PS)	57	1.59	2.65	P < 0.001
My child has mastered basic culinary skills (PS)	53	1.57	2.81	P < 0.001

*P < 0.001613. McNemar-Bowker Test

** Mean Responses based on a 1-3 scale; 1 = disagree, 2 = so-so/neutral, 3 = agree

***SC = Skills Checklist; PS = Parent Survey

Change in knowledge

All 23 metrics used to determine change in knowledge/skill demonstrated a statistically significant increase (Table 1); a positive change in culinary knowledge was identified. Overall, the measures used to assess this objective demonstrated a strong increase in culinary and nutritional knowledge

Change in attitudes

Of the six outcomes measured to assess a change in attitude, three were statistically significant (Table 2); it is therefore difficult to determine if a change in attitudes occurred though a positive trend signifying improvement was noted. Parents and children agreed that following workshop completion, the children were better equipped to make healthy choices. The parents and children disagreed regarding fruit and vegetable consumption: parents noted a statistically significant increase in the quantity of fruits and vegetables consumed by their child, whereas the children did not. Interestingly, both parents and children agreed that the child was no more willing to try new foods at the end of the workshops than the beginning. Additionally, a post-workshop-only question for parents showed that 61% of parents believed their child had tried a new food at home since the beginning of the workshop.

Table 2. Quantitative results for objective two (change in attitudes from pre-workshop to post-workshop). Three of six measures showing statistically significant improvement over the course of the workshops; some disagreement is noted between parents and children regarding fruit and vegetable consumption. The other two measures showing agreement between parent and child.

Metric	n (matched)	Mean Pre-Workshop Response	Mean Post-Workshop Response	p-value
I eat lots of vegetables and fruits (SC)	175	2.70	2.75	0.62
I know how to make healthy food choices (SC)	178	2.41	2.79	P < 0.001
I am open to trying new foods (SC)	183	2.68	2.73	0.46
My child eats plenty of fruits and vegetables (PS)	57	2.20	2.72	P < 0.001
My child knows how to make healthy food choices (PS)	57	2.41	2.84	P < 0.001
My child is open to trying new foods (PS)	57	2.69	2.67	0.46

*P < 0.001613. McNemar-Bowker test.
** Mean Responses based on a 1-3 scale; 1 = disagree, 2 = so-so/neutral, 3 = agree
***SC = Skills Checklist; PS = Parent Survey

Change in behaviour

Change in behaviour was assessed by one question administered to both parents and children asking about perceived frequency of cooking together at home (Table 3). Only the parental responses indicated a statistically significant improvement; it is therefore difficult to determine if an overall change in behaviour occurred, though there was a positive trend identified. Interestingly, the child responses did not change appreciably while the parents indicated in the pre-post question *and* in the post-workshop-only question that they cooked often/more often with their child (63% of parents agreed/strongly agreed with the statement: "Since the beginning of BàL, my child and I cook more together").

Table 3. Quantitative results for objective three (change in behaviour from pre-workshop to post-workshop). Only the parental response showed a statistically significant improvement in culinary behaviour over the course of the workshop; while the child response was in the positive direction, this is not conclusive.

Metric	n (matched)	Mean Pre-Workshop Response	Mean Post-Workshop Response	p-value
I cook often with my parents/family (SC)	178	2.34	2.50	0.092
My child and I cook together at home (PS)	57	1.81	2.43	P < 0.001

* P < 0.001613. McNemar-Bowker test.
** Mean Responses based on a 1-3 scale; 1 = disagree, 2 = so-so/neutral, 3 = agree
***SC = Skills Checklist; PS = Parent Survey

Discussion

BàL is an NCEP running in Montréal since 2003; in this time, no formal evaluation was undertaken to confirm that objectives were being met. The present study used models similar to ones in the literature to perform an evaluation using secondary data collected by BàL and demonstrated the effectiveness of the program in improving the culinary skill and knowledge of the children. While only half of the questions used to assess two of the main objectives (changes in attitude and behaviour) showed statistically significant improvements, the directions of all but one change were positive. The number of questions used to address each objective was determined based on questions already included in the questionnaires; the questions were chosen based on the stated objectives and were not modified for the purposes of this research. To further elucidate possible changes in both attitudes and behaviour, future studies could include more questions that specifically address these objectives. In addition to the pre-post questions, two post-workshop-only questions suggest that an improvement in attitude and behaviour have been met i.e.: 61% of parents indicated that their child had tried a new food at home since the

beginning of the workshops, and 63% of parents felt they cooked more with their child following the program.

While these final two metrics are not necessarily indicative of a change attributable to BàL, they are interesting for other reasons. The first question ("Has your child tried a new food at home since the beginning of BàL") is the only question posed that uses a yes/no response and is objective in nature (and 61% said yes). While there are similar questions on both questionnaires that ask about willingness to try new foods, they give no standardized way for respondents to quantify willingness. The questions used by this study to assess willingness are similar to others used in the literature, such as agreement statements ("my child is constantly sampling new and different foods")[14] and questions asking about perceived willingness,[14]. For this reason, even considering the lack of pre-post comparison, this question holds some value in the context of a program evaluation. In future questionnaires, a baseline question should be added that asks whether the child has tried new foods in the 10-weeks prior to the commencement of the workshops, which can then be compared to the number at the completion of the workshop.

The latter question asked parents about the perceived frequency of cooking with their child; the results are in agreement with the related question on the parental pre-post-test ("My child and I cook together at home") that demonstrated a statistically significant change ($p = 3.00 \times 10^{-6}$). However, the companion child question ("I cook more with my family") did not yield a significant change between pre- and post-test. This disparity raises interesting considerations regarding data sources. When utilizing data from multiple related sources from similar tools and metrics, as seen here with parent and child data, interpreting results can be arduous[16]. It is made even more difficult when the sources are related yet occupy specific social roles; family members may understand and recognize different subjective realities, and there may be distinct interests of each family member (i.e. self-serving bias of parents wanting to appear as good parents)[16,17]. A 2018 study investigating the validity of parent and child questionnaires showed that parents often report more positive claims regarding their own parenting compared to reports from their children[16]. While it is beyond the scope of this study to decipher the intricacies of parent-child perspectives and perceptions, it begs further investigation as there appears a paucity of data suggesting methods for reconciliation of the two perspectives.

Overall, the results observed by the present study are in agreement with other studies in the literature that suggest an improvement in culinary skill and a trend towards improvements in attitudes and behaviours[1-3,6,8,11]. This study reaffirms that NCEPs are effective in increasing the culinary skillset of youth and may incite positive benefits in related areas of culinary attitudes and behaviours . Based on the results of various research studies, culinary skill is a large contributing factor to lifelong dietary habits. Interventions aimed at improving the culinary skill of participants may therefore lead to more nutritious diets throughout life. Further research is needed to fully elucidate the possible benefits of culinary and nutritional intervention programs, such as BàL, in changing the lifelong habits of participants.

Implications

This study demonstrates that it is possible to implement, evaluate, and adjust running NCEPs. Many NCEPs are designed to fill a need in a community or school and are not designed in the context of a scientific study; as such, by presenting the methodology used here, researchers and workshop coordinators in similar positions may find useful directions to shape their programs to reach similar goals. While it is optimal to construct evaluations and prepare for scientific inquiry during initial program planning, it is not always possible nor required. This study shows, through the demonstrated improvement in culinary skill, that adaptation of what is available and implemented elsewhere is both a practical and efficacious method of operation.

Furthermore, this study adds to the knowledge base investigating and supporting the use of NCEPs in children. Firstly, the use of both parental and child data allows for the comparison and corroboration of how the child's abilities and behaviours are perceived by the child himself/herself, and by the child's parents. The use of comprehensive and similar parental and child data has rarely been done in the literature and allows for in-depth assessments of the intricacies of perceived changes and raises further questions regarding how to interpret differences.

Limitations and suggestions for future planning

This study contains limitations that must be addressed. First, is the lack of control group and the inability of a retrospective study to demonstrate causation. It is the belief of the researchers that the Hawthorne Effect would have been minimal, as the questionnaires were administered as part of standard practice and not in the context of research with an observer[18]. Nevertheless, the lack of control group prevents the formation of definitive conclusions regarding the results observed. Additionally, the present study relies heavily on data collected from children. Data collected from children regarding self-behaviours may suffer biases and may be unreliable; however, the present study requires this data and accepts any limitations inherent to it.

Additionally, no formal piloting of questionnaires occurred, and internal and external validity have not been demonstrated; this may have affected the ability of the parents and children to understand and interpret the questions. However, the unique questionnaires have been administered, in one form or another, to over 1500 children and have evolved periodically to ensure that program objectives were being met. Future evolutions of the questionnaires will be adapted to include more objective language where previous iterations used vague, subjective language (ex: "plenty", "often", "cook"). Future iterations of the questionnaires may include a condensed version of a Food Frequency Questionnaire or Dietary Recall, as seen in other studies, to decrease the subjectivity of the results[4,12.] To reduce the biases inherent to these tools, a three-day recall completed by parent and child could be completed. An additional question addressing the frequency of home meal preparation may also be included to assess familial routines and cooking opportunities.

Finally, the authors recommend methods for increasing the collection of viable data. In the present study, viable data was lost due to the evolution of the surveys over time, the use of group-level data in the place of individual raw data protected by unique student identifiers, and attrition in the parental cohort. A study by Bastaists et al. investigating adult non-response with child perspective data found that major indicators of whether a child completes a survey are: the topic of the survey, child demographics (lower education and ethnic minorities have been shown to respond less to surveys), and parent-child relationships (more supportive parents are more likely to participate than less supportive parents)[17]. Relating to the current study, parents who fill out the surveys are likely to be more engaged in their child's activities, both within and outside of the BàL workshops. Selection bias may have factored into the responses given by parents and children, especially considering that only 1/3 of the parents completed the questionnaires. As such, future directives should include measures to increase parental post-survey response rates, such as a dedicated time at the end-of-session party to fill out the forms or notes sent home with the children at the final workshop to better capture input from all parents.

Implications for research and practice

NCEPs of sufficient frequency and duration have proven repeatedly to be effective in increasing nutrition and culinary knowledge, increasing culinary self-efficacy, and fostering healthy food relationships[5,6,8,11,12,14]. This study confirms the power of these programs to increase the culinary knowledge base and skillset of children. The present study was not able to demonstrate a clear improvement in attitudes or behaviours and future research is needed in these areas. Furthermore, while evaluation methods are an integral component of program planning, the present study demonstrates that evaluation tools can evolve with NCEPs and still be effective. The gold standard is not always feasible in real-world interventions; often, objectives can be met in other ways.

Conclusion

Hands-on nutrition and culinary skills education programs, like BàL, are effective interventions to improve the culinary skillset of children. Subjective changes that result from these programs, such as changes in attitudes and behaviour, are difficult to assess; while this study found a positive trend, overall scores in these categories were not definitive and future research is needed.

Acknowledgements

The authors would like to thank Dr. Jose Correa at the Statistical Consulting Service of McGill University for his advice and guidance relating to the statistical analyses of the present study.

References

1. Chu Y, Storey K, Veugelers P. Involvement in meal preparation at home is associated with better diet quality among Canadian children. J Nutr Educ Behav. 2014 Jul;46(4):304-8. 1.
2. Hodges C, Roseno A, Duffrin M, Stage V. Middle school nutrition knowledge tool development and evaluation in North Carolina. Food Sci Nutr. 2017 May;47(3):332-345.
3. Jarpe-Ratner E, Folkens S, Sharma S, Daro D, Edens N An experiential cooking and nutrition education program increases cooking self-efficacy and vegetable consumption in children in grades 3-8. J Nutr Educ Behav. 2016 Nov;48:697-705.
4. Larson N, Perry C, Story M, Neumark-Sztainer D. Food preparation by young adults is associated with better diet quality. J Am Diet Assoc. 2006 Dec;106:2001-2007.
5. Nelson S, Corbin M, Nickols-Richardson S. A call for culinary skills education in childhood obesity-prevention interventions: Current status and peer influences. J Acad Nutr Diet. 2013 Aug;113(8):1031-1036.
6. Zahr R, Sibeko L. Influence of a school-based cooking course on students' food preferences, cooking skills, and confidence. Can J Diet Prac Res. 2017 Mar;78(1):37-41.
7. DeCosta P, Moller P, Frost M, Olsen A. Changing children's eating behaviour – A review of experimental research. Appetite. 2017 Jun;113(1):327-357.
8. Condrasky MD, Quinn A, Cason K. Cooking camp provides hands-on nutrition education opportunity. J Culin Sci Tech. 2007 Sep;5(4):37-52.
9. Hingle M, O'Connor T, Dave J, Baranowski T. Parental involvement in interventions to improve child dietary intake: A systematic review. Prev Med. 2010 Aug;51(2):103-111.
10. Battjes-Fries M, Haveman-Nies A, van Dongen E, Meester H, van den Top-Pullen R, de Graaf K, et al. Effectiveness of taste lessons with and without additional experiential learning activities on children's psychosocial determinants of vegetables consumption. Appetite. 2016 Oct;105:519-526.
11. Cunningham-Sabo L, Lohse B. Cooking with Kids positively affects fourth graders' vegetable preferences and attitudes and self-efficacy for food and cooking. Child Obes. 2013 Dec;9(6):549-556.
12. Wrieden W, Anderson A, Longbottom P, Valentine K, Stead M, Caraher M, et al. The impact of a community-based food skills intervention on cooking confidence, food preparation methods and dietary choices – an exploratory trial. Public Health Nutr. 2007 Feb;10(2):203-211.
13. Oshaug A. Evaluation of nutrition education programmes: Implications for programme planners and evaluators. Paper presented at: Nutrition Education for the Public. FAO Expert Consultation, September 1997; Rome, Italy. http://www.fao.org/docrep/W3733E/w3733e06.htm#evaluation%20of%20nutrition%20education%20programmes:%20implications%20for%20programme%20planner. Accessed

April 14 2018.
14. Allirot X, Da Quinta N, Chokupermal K, Urdaneta E. Involving children in cooking activities: A potential strategy for directing food choices toward novel foods containing vegetables. Appetite. 2016 Aug;103:275-285.
15. Huitema B. The Analysis of Covariance and Alternatives: Statistical Methods for Experiments, Quasi-Experiments, and Single-Case Studies. Chicester: Wiley; 2011. 544 p.
16. Cole D, Goodman S, Garber J, Cullum K, Cho S-J, Rights J, et al. Validating parent and child forms of the Parent Perception Inventory. Psychol Assess. 2018 Aug;30(8):1065-1081.
17. Bastaits K, Pasteels I, Ponnet K, Mortelmans D. Adult non-response bias from a child perspective. Using child reports to estimate father's non-response. Soc Sci Res. 2015 Jan;49:31-41.
18. Monahan T, Fisher J. Benefits of "Observer Effects": Lessons from the field. Qual Res. 2010 Jun;10(3):357-376.

Commentary

Early exposure to community service learning in the medical curriculum: A model for orientation week

Kaitlin Endres

University of Ottawa, Ottawa, Canada

Abstract

Community service learning programs in pre-clerkship medical education are increasingly recognized as important in creating physicians who recognize the effects of one's environment on their health and further strive to advocate for these patients to receive access to social programs that can improve their outcomes. The University of Ottawa Aesculapian Society recognized that an excellent method for providing early exposure to service opportunities in one's new community is through Orientation Weeks. Prior to this year, no Orientation Week across Ontario had a philanthropy focus. Philanthropy in most students' eyes refers to monetary donation. Understandably, Orientation Week directors continuously make the decision that asking medical students to donate money during the first week of one of many financially demanding yeas is unrealistic. Ottawa decided to incorporate philanthropy into our Orientation Week in the more inclusive form of community service, allowing students to donate their time, rather than donating their money. In addition to ensuring that philanthropy still has the opportunity to be a fundamental component of bonding during Medical School Orientation Weeks, as it does at the Undergraduate degree level, our initiative also served to facilitate early exposure to the various organizations students could complete their community service learning placements with later in their first year. Here we present our model, uO-Serves ("uOttawa-Serves") of an Orientation Week philanthropy initiative of time-based community service in hopes that other Medical Schools will consider implementing a similar initiative within their Orientation Weeks

Keywords: community service learning, orientation week, philanthropy, volunteerism

Corresponding author: kendr071@uottawa.ca

Introduction

As medical students transition into medical practitioners, they will encounter a growing number of patients whose health problems are related to their surroundings. Consequently, medical students must be prepared to mitigate the effects of a multitude of environmental factors on the health of their patients, and therefore medical school curricula must integrate pedagogical strategies to help future physicians understand and address these modifiable social determinants encountered by community members[1-3]. In response, Canadian medical schools are increasingly incorporating Community Service Learning (CSL) programs into their curricula. CSL aims to educate medical students through active involvement in their community, rather than through conventional lecture-based learning[4-6]. These programs help students broaden their knowledge about the impact of the social determinants of health on their future patients, while providing aid to community members in need. CSL programs further develop participants' critical thinking, problem-solving and communication skills[1,7]. Additionally, CSL increases students' understanding of social concepts learned in class, allowing students to apply theory to real-life situations, and further enhances one's social awareness and responsibility[8].

Unfortunately, increasing numbers of medical students view these CSL programs primarily as a mandatory requirement for earning a medical degree, rather than an opportunity to learn skills necessary for their future career as physicians[9,10]. As the Vice-President (VP) Philanthropy of the Aesculapian Society (ASOC) at the University of Ottawa (uOttawa), I posited that the absence of *early exposure* to community service opportunities throughout the medical curriculum contributed to uOttawa students' decreased enthusiasm for CSL programs. I felt that an early positive volunteering experience would not only promote bonding with their new peers while giving back to their community, but would also be beneficial for students by helping build excitement about the CSL placement they would be required to complete throughout first-year. Further, I believed this experience would allow students to discover what they enjoyed and what they disliked, about their volunteer opportunity. Currently, at most medical schools, students rank their placements using an online system using a brief description of the organization for their decision making[4-6]. For medical students who have moved to a new community to complete their medical education, it is difficult to know which placement/organization best aligns with their interests. By integrating participation in community activities into O-week, students were provided with early exposure that would allow them to get a better idea of where they would like to volunteer later in the year. While many Ontario medical schools do not include philanthropic programming in their O-Week, I proposed that rather than focusing on monetary donation, students could be asked to donate their time. I believed that this would not only allow philanthropy to have a presence during O-Week, but also facilitate early exposure to CSL placements.

For the first time ever, our ASOC VP Philanthropy portfolio implemented an event called "uO-Serves" ("uOttawa-Serves") for uOttawa O-Week 2018. This involved first- and second-year medical students aiding various organizations in Ottawa by volunteering their time. uO-Serves appears to have had a positive impact on how students view CSL within the medical education curriculum and proves support for approaches that place an emphasis on community service and volunteerism from the start of students' medical education. This is evidenced below through unsolicited participant testimonials as

well as student interest in creating more long-term opportunities through further expansion of uO-Serves.

Community service learning programs in medical curricula

By facilitating students' understanding of the social roles that come along with their future profession, Eckenfels argues that community service experiences that allow medical students to aid those in need broaden students' education and offer a perspective of health and illness that the classroom cannot, fostering relationships with the community they will be helping serve[11]. Students gain insight into how health promotion interventions and community partnerships can improve health disparities[8]. CSL programs exist at the majority of Canadian medical schools and allow students to contribute to their communities and then produce a corresponding reflective assignment on the topic[7]. A student's CSL experience allows them to explore connections between classroom learning and the experiential learning they are doing in the community, providing the opportunity to contextualize their roles as citizens and professionals through real-life experiences. CSL programs not only benefit the medical students who participate in them, but also provide community organizations with additional human resources, allowing tasks to be accomplished that may otherwise not have been possible, such as large-scale environmental clean up or donation sorting[12].

CSL provides a tangible experience to students allowing them to integrate traditional academic learning with immediate, hands-on practical experience[4]. There is much diversity in accepted CSL projects, but they often involve teaching, healthcare, community development, environmental projects or another avenue that contributes to the well-being of individuals or local communities**.** Due to the longitudinal nature of CSL projects, they challenge medical students to understand the community organization's philosophy, values, mission and the living conditions of the organization's clients[9]. The key aspect of service learning is its mutual reciprocity; the student learns from the service agency and the agency learns from the student through the unique perspective they bring from their classroom learning[3]. While many medical students come into medicine with altruistic motives; few carry this altruism into their practice[13]. Teaching social accountability is expected to help students remain altruistic and stay engaged in community work, in addition to further encouraging work in underserved areas, such as rural communities[13, 14].

uO-Serves Model

At the non-medical undergraduate education level, O-Week primarily focuses on philanthropy through monetary donation to an organization in need, such as "Shinerama", which supports cystic fibrosis research[15-18]. Uniquely, uOttawa is the only Ontario medical school with a strong philanthropy presence during O-Week. Many previous and prospective O-Week Directors at other medical schools attribute the lack of philanthropy programming to increasing costs of medical school tuition combined with already expensive O-week fees, making fundraising during O-Week an understandably tough ask of first-year medical students[19-22].

Previously, uOttawa focused their philanthropy efforts *strictly* on monetary fundraising for Shinerama. As students, we are not always in a position to be able to donate our money to philanthropic efforts; however, most students are able to donate time. Therefore, I felt student engagement would increase if we expanded our O-Week philanthropy focus from fundraising alone, to the inclusion of volunteerism activities that provided an opportunity for students to give back. With this goal in mind, as well as the hope of inspiring other medical schools to incorporate philanthropy into their O-Weeks, uO-Serves was created.

Figure 1. O-week students at the Ottawa Food Bank Community Harvest Program.

All 12 O-week teams of students were assigned to 12 different organizations across Ottawa including The Ottawa Mission, Ottawa Food Bank Community Harvest Program, Habitat for Humanity, Ottawa Salivation Army Booth Centre, StopGap, Canadian Blood Services, Ronald McDonald House, Shepherds of Good Hope Shelter, Boys and Girls Club of Ottawa and the AIDS Committee of Ottawa. The ASOC worked with various organizations to ensure that the task was low-risk enough that it still allowed students to bond with their peers on the first day of O-Week and yet significant enough that it

helped the organization and their clients. From serving a meal at Shepherds of Good Hope, to helping make Ottawa more accessible by building ramps with StopGap, to harvesting crops at the Ottawa Food Bank's Community Harvest Program shown here in Figure 1, for the first time at uOttawa Medicine students were not only able to contribute to O-Week philanthropy efforts by donating their money to our Shinerama campaign, but were provided with the alternative option of donating their time[6]. uO-Serves has now been unanimously voted into our constitution by all elected ASOC members as a yearly philanthropic initiative during each future O-Week. Further, first-years were inspired to transform uO-Serves into a long-term commitment through a proposal to establish a new Community Service Interest Group for Fall 2019. One first-year student believes that "through uO-Serves and the friendships it helped foster, I believe our VP Philanthropy changed many students from viewing CSL volunteerism as a mandatory part of their first-year experience, to instead viewing the curriculum as a unique and exciting opportunity that they were excited to participate in." A second-year student was able to "witness first-hand how this initiative allowed first-year students to sample local programs and consider which aspects they might be passionate about, undoubtedly helping them in selecting their future CSL placements." Future directions for uO-Serves include completing a more objective study to measure the impact of the initiative on students' perceptions of volunteerism in medical school. Through a quality improvement project for the VP Philanthropy portfolio, ASOC members plan to further validate these claims and identify areas for advancement through use of a formal feedback survey following uO-Serves 2019.

Conclusion

Incorporating community service into O-Week facilitates early positive exposure to community service organizations in the medical school curricula and allows for students to bond with their peers over the rewarding sense of giving back to their new shared community. Further, an initiative like uO-Serves, which focuses on students giving back their time as opposed to money, supports a more inclusive way for students to give back, regardless of financial background. By integrating CSL placements early on in a non-threatening environment it provides students with the chance to explore volunteer options to better prepare them for when they have to make placement decisions later in their first year at a time when they are under increased stress. It has been well established that CSL placements are a vital educational tool that have been incorporated into medical curricula across many Canadian medical schools[4-6]; however, it is likely that without early, first-hand exposure to community service opportunities available in students' new communities, we are failing to set up medical students to find these programs as valuable as they could be.

Acknowledgements

I would like to thank our ASOC VP Social Sam Wilson for all his support in allowing me to incorporate uO-Serves into his O-Week programming. I would additionally like to thank ASOC's VP Executive Jessica Tao for her encouragement to establishing uO-Serves here at uOttawa as well as Mehr Jain,

ASOC's VP External for her help in sharing this initiative with other medical schools across the province.

References

1. Stewart T, Wubbena Z. An overview of infusing service-learning in medical education. Int J Med Educ 2014; 5: 147-56.
2. Burrows MS, Chauvin S, Lazarus CJ, et al. Required service learning for medical students: Program description and student response. Teach Learn Med 1999; 11: 223-31.
3. Averill NJ, Sallee JM, Robinson JT, et al. A first-year community-based service learning elective: design, implementation, and reflection 2007; 19: 47-54.
4. Michaëlle Jean Centre for Global and Community Engagement, University of Ottawa. (no date). Community Service Learning. Retrieved Dec 18, 2018 from the Word Wide Web: https://servingothers.uottawa.ca/volunteering/community-service-learning.
5. Dr. Teresa VanDeven, Schulich School of Medicine & Dentistry. (2016). Service Learning in Undergraduate Medical Education. Retrieved Dec 18, 2018 from the World Wide Web: https://www.schulich.uwo.ca/medicine/undergraduate/academic_resources/service_learning.html
6. Queen's UGME, Queen's University (2016). The Service Learning Program at Queen's School of Medicine. Retrieved Dec 18, 2018 from the World Wide Web: http://www.intlmeds.queensu.ca/blogs/2016/11/19/service-learning-program
7. Arora N, Ngo K, Weerakkody I, Doshi S and Khan R. Ontario Medical Student's Association. Improving Service Learning in Medical Education. (2017). Retrieved Dec 19, 2018 from the World Wide Web: https://omsa.ca/sites/default/files/position_paper/43/position_paper_improving_service_learning_curricula_in_medical_education_2017_mar.pdf.
8. Buckner AV, Ndjakani YD, Banks B et al. Using service-learning to teach community health: the Morehouse School of Medicine Community Health Course. Acad Med 2010; 85: 1645-51.
9. Adela Talbot, Western News. Bringing holistic health to the community (2018). Retrieved Dec 18, 2018 from the World Wide Web: https://news.westernu.ca/2018/03/bringing-holistic-health-community/.
10. Loh AZH, Tan JSY, Lee JJM and Koh GCH. Voluntary community service in medical school: a qualitative study on obstacles faced by student leaders and potential solutions. Glob Health Action 2015; 8: 10.3402/gha.v8.27562.
11. Eckenfels, EJ. Contemporary medical students' question for self-fulfillment through community service. Acad Med 1997; 72: 1043-1050.
12. McLaughlin JE, Roth MT, Glatt DM et al. The flipped classroom: a course redesign to foster learning and engagement in a health professions school. Acad Med 2014; 89: 236-243.
13. Salas AA, Anderson MB, LaCourse L et al. CurrMIT: a tool for managing medical school curricula. Acad Med 2003; 78: 275-9.

14. Meili R, Fuller D, Lydiate. Teaching social accountability by making the links: qualitative evaluation of student experiences in a service-learning project. Med Teach 2011; 33: 659-666.
15. No Author. Laurier University. Laurier welcomes first-year students to Brantford with a week of orientation events. (2017). Retrieved Mar 30, 2019 from the World Wide Web: https://www.wlu.ca/news/news-releases/2017/sept/laurier-welcomes-first-year-students-to-brantford-with-a-week-of-orientation-events.html.
16. No Author. Guelph Tribune. Shinerama back after 10 year absence. (2012). Retrieved Mar 30, 2019 from the World Wide Web: https://www.guelphmercury.com/community-story/5864171-shinerama-back-after-10-year-absence/.
17. No Author. University of Toronto. UTSC Shinerama. (2019). Retrieved Mar 30, 2019 from the World Wide Web: https://www.ulife.utoronto.ca/organizations/view/id/126931.
18. Shinerama. Cystic Fibrosis Canada. (2019). Find Your School. Retrieved Apr 01, 2019 from the World Wide Web: http://shinerama.ca/#school.
19. Orientation Planning Team Members. University of Toronto. (2018 and 2019). (December 30, 2018). Personal Interview. (December 30, 2018). Personal Interview.
20. Orientation Planning Team Member. Queens University. (2019). (December 31, 2018). Personal Interview.
21. Orientation Planning Team Members. Western University. (2018 and 2019). (December 30, 2018). Personal Interview.
22. Orientation Planning Team Members. University of Ottawa. (2017, 2018). (December 29, 2018). Personal Interview.

Original Research Article

Feasibility of standardizing pre-operative assessment clinics across a hospital system

Megan E. Brown[a], Cameron F. Leveille[b], Jean Paul Paraiso[c], David Nykolaychuk[c], and Madelyn P. Law[a]

[a] Faculty of Applied Health Sciences, Brock University, St. Catharines, Canada

[b] Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Canada

[c] Niagara Health, St. Catharines, Canada

Abstract

Pre-operative assessments, which include patient history and physical examination, are fundamental in ensuring patient education about their procedure, and leads to successful post-operative outcomes. Within Niagara Health (NH), there are three main hospital sites where operations occur. Currently, there is inconsistency in the pre-operative assessments between sites for the same surgical procedures, demonstrated by variation in pre-operative assessment times, activities, and information given to patients. The aim of this project is to understand where standardization through quality improvement (QI) initiatives should begin within these pre-operative assessment clinics and determine the feasibility of standardization across varying hospital sites. To achieve this aim, Plan, Do, Study, Act (PDSA) cycles were conducted and involved structured observations at each site to gain a comprehensive understanding of pre-operative practices across sites. Root cause analysis found moderate correlation at two sites and strong correlation at one site between patient age and consult time. Affinity analysis determined that the most pragmatic and feasible area for improvement was through standardization of admission history forms. While the piloting of a new standardized form showed no significant increase in consult times, fundamental barriers such as nursing staff turnover, lack of familiarity with the new form, and concerns of comprehensiveness prevented the continuation of this new standardized form. Future attempts at standardization should begin with collaboration and co-design with pre-op clinic staff, followed by identification of elements of the complex adaptive system that can feasibly be standardized to reduce unnecessary variation while at the same time increasing buy-in for form use.

Keywords: Pre-operative assessment, Quality improvement, Standardization, Co-design, Surgery

Corresponding author: mlaw@brocku.ca

Introduction

Pre-operative assessment clinics (PACs) are designed to improve efficiency, provide surgical information to patients, and promote improvement in post-operative outcomes; however, lack of standardization across institutions within the same healthcare system prevents these clinics from achieving optimal efficiency and patient satisfaction. Currently, there is inconsistency in the pre-operative assessments between three sites within the Niagara healthcare system for the same surgical procedures (i.e. urology, orthopedic, gynecological, and diagnostic surgical procedures). These inconsistencies include variation in pre-operative assessment times ranging anywhere between 20-45 minutes, assessment forms used by nursing staff, and information given to patients.

These inconsistencies can carry consequences that are reflected in every stakeholder group involved in the operation of PACs. At a higher level, these consequences include redundancy in information, such as prescriptions, longer patient wait-times, and increase in the potential for error that can negatively impact patient safety in the operating room (1). Lack of standardization in these Niagara PACs limits portability of care for patients, creating an inconvenience as well as preventing accessibility of patient information that is able to be collected at other Niagara Health (NH) sites – an element that can often pose frustration for patients accessing care at multiple sites. Unstandardized practices also impact staff function and burnout, particularly for nursing staff who must manage increased patient volumes in pre-op clinics. Lastly, one important additional consequence of inconsistency across PACs is the resulting variation in presentation and interpretation of clinical information by surgeons and other health care professionals who often rotate through and perform surgery at each of the three sites (1-2). Overall, the functioning of PACs may benefit from standardization, improved process, and new policy implementations in order to achieve higher satisfaction for patients and healthcare providers as well as reduce costs and shorten hospital wait-times. However, executing these goals can be difficult given the aforementioned complex adaptive nature of health institutions, the many stakeholders involved, the amount of effort required to implement and change processes, and the overall feasibility for such an undertaking.

As a starting point, the Choosing Wisely Canada Toolkit is a guideline designed to reduce unnecessary visits and investigations in pre-operative clinics and provides physician groups and organizations with an outline to optimize the pre-op process (3). Within this toolkit is a pre-op clinic consultation guideline which outlines which patients should be referred to the pre-op clinic for a consultation by their surgeon's office. For the surgeon to make this decision, complexity of the surgery and/or patient factors such as age, and co-morbidities, must be accounted for (3). The implementation of this toolkit and pre-op consultation guideline would reduce the number of lower-risk patients attending the clinic, and result in a shift in the overall patient population of the clinic towards higher-risk categories. Thus, the case-mix of the patient population attending the clinic will change (3).

To this end, the project presented focuses on developing a standardized pre-operative assessment for each of these three surgical sites within Niagara Health based on the Choosing

Wisely Canada framework. Overall standardization will ensure consistency, safety and efficiency for patients and health professionals. As such, the aim of this project was to understand where standardization through QI initiatives should begin within the pre-operative assessment clinics, identify any possible interventions based on stakeholder analysis, and to determine the feasibility of standardization across varying hospital sites in this local region.

Methods

This QI project utilized Plan, Do, Study, Act (PDSA) cycles, which are a series of short-cycle, small-scale tests of change linked to assessment of each cycle's outcomes (4). PDSA cycles allow for low-risk tests of change based on input from front line staff and may therefore encourage useful staff engagement in quality improvement (4). In the context of this study, PDSA methodology was beneficial because the framework helps the user to understand the impact of small-scale interventions and the natural variation within a system through the measurement of data over time (5).

PDSA cycle 1: root cause analysis to determine the factor(s) contributing to the lack of standardization.

Structured observational visits were conducted at each site where patients were asked for consent to be followed through their pre-operative clinic consults. Ten patients were followed through their nursing consult at site A, eleven patients at site B, and ten patients at site C. Additionally, two of the patients at each site were followed through the entire process from check-in, visits with the nurse, anesthesiologist, occupational therapist, physiotherapist, and through their diagnostic testing and imaging procedures. This was done at each site to gain a comprehensive understanding of the flow in the pre-operative assessment clinic.

A structured observation tool was used to observe for patient, physical, and organizational factors which were hypothesized to contribute to the lack of standardization. This tool was created as a sensitizing framework from which to observe for specific activities (5). Patient factors included complexity of cases, type of surgery, and age. Physical factors included physical design and architecture of the pre-operative assessment clinic, assessment instruments available (i.e. ECG machine), and assessment forms filled out. Organizational factors included the number of staff and the types of surgery conducted at each site. The observers using this framework were cognizant of the fact that other valuable information may be present in the environment and therefore remained open to other important material that was outside of this observational tool (6).

PDSA cycle 2: focus group to identify feasible intervention.

A focus group with the chief of surgery and nurses from each hospital site was held, where an affinity analysis was conducted using the following guiding questions: What is the level of readiness to change within your PAC? In one year, what would you like to see done? What can we do to make the process more efficient, effective and better for staff and patients? This meeting was conducted to determine the most appropriate scope and focus for the QI project.

Attendees were presented with the current local problem and were instructed to use these guiding questions to come up with one long-term change and one short-term change that could be implemented within their hospital site's PAC. Common themes from each focus group were identified and utilized to determine an intervention that would be both feasible and relevant across all sites.

PDSA cycle 3: development and implementation of a standardized nursing assessment form.

Short-term common themes identified in PDSA cycle 2 were used to guide the course of intervention. It is protocol within NH to trial a paper copy of the new assessment form before building it into the Meditech system at the two other sites that currently use paper nursing assessment forms.

A standardized nursing assessment form was created using the Meditech computerized form from site A as a template (Appendix 2). The form was finalized by the nurse managers of each pre-op clinic and sent to a forms committee for approval prior to going live at sites B and C. Feedback forms were given to the pre-op nurses at each of these sites as a balancing measure to assess their satisfaction and to document any subsequent changes that should be made to the new assessment form. They were also instructed to document the duration of time and type of surgery for each consult that took place over the week.

Results

PDSA cycle 1: root cause analysis to determine the factor(s) contributing to the lack of standardization.

The pre-operative clinic activities performed at each site gathered the same information (i.e. patient history, standardized anesthetic patient record filled out); however, the method by which the information was documented varied. The most prevalent difference was the variation in nursing assessment forms used and the way in which the nurses documented patient information. There was a computerized nursing assessment on Meditech at site A and paper assessment forms that were completed at sites B and C.

Although not significant at each site, nursing consultations for in-patients required more time than out-patients (Figure 1). This can be attributed to the increased complexity of in-patient surgery compared to outpatient surgery. There were significant differences in consultation times between site A and site B for both in- and out-patients, which can be attributed to the complexity of the procedures done at each hospital. There was a strong correlation between patient age and consult time at site A, with an r-value of 0.77 (Figure 2). At site B and site C, there was a moderate correlation between patient age and consult time, with r-values of 0.52 and 0.58, respectively (Figure 3,4).

Physical factors including design and architecture of the PAC and assessment instruments available (i.e. ECG machine) were also different at each site. However, only site A conducted ECGs within the nursing consult, whereas laboratory technicians performed this test separately at the remaining two sites. This process added time to the nursing consult at site A. Additionally, there were more examination rooms for consultations to take place at site A, whereas the remaining sites only had one room to conduct all pre-operative nursing consultations. An additional layer of complexity was added since site A had four to five pre-op nurses conducting consultations whereas site B and site C only had one pre-op nurse who conducted consultations.

Based on nurse feedback and the small sample of patients that were followed at each site, the time that each consultation takes is dependent upon the status of each individual patient. As outlined by the nurses throughout the observational visits, they felt that polypharmacy, additional comorbidities, and level of patient education received prior to pre-op all contributed to the nursing consult time, making it difficult to standardize the consultation times across each site.

PDSA cycle 2: focus group to identify feasible intervention.

The following long-term changes were identified through the affinity analysis conducted at the focus group: best possible medication history (BPMH) should be typed into a computer then printed for the patient chart, mandating pre-op for all patients, and frequency of anesthesia presence in the clinic. Additionally, the following short-term changes identified were: computerization of patient history and an updated computer system, updating of the patient history form in Meditech, and standardization of admission history forms (Appendix 1).

Medication reconciliation is currently in a phase of QI at NH and anesthesia schedules are highly inconsistent across the sites. These long-term changes are primarily related to staffing, which is a complex area that is out of the scope of this QI project. Within the time that the structured observational visits in PDSA cycle 2 took place, there were pharmacist cutbacks in the pre-operative assessment clinics, who historically conducted the BPMH. Anesthesia schedules had also changed. Therefore, due to the complexity of these two areas of the pre-operative process, it was more feasible to hone in on the short-term changes involving the standardization of nursing consults.

The most prevalent common themes that arose from the affinity analysis were the large amount of paperwork and the lack of standardization of the nursing pre-op assessment forms.

Based on the short-term results of the affinity analysis, it was evident that the course of intervention should focus on the standardization of nursing assessment forms (Appendix 1). As mentioned previously (2), standardized assessment forms improve the quality of information recorded, and thus, validates the course of intervention trialed in PDSA cycle 3.

PDSA cycle 3: development and implementation of a standardized nursing assessment form.

New form data was provided by the nurse for day surgery consults at site C, which showed that there was no statistically significant difference in the median nursing consult time before and after the implementation of the new standardized assessment form (Figure 5). Upon further feedback given by the nurses, nurse managers, and clinical educators, the use of the new form was stopped after one week to undergo further edits and review due to conflicting opinions and concerns with the comprehensiveness of the information being collected.

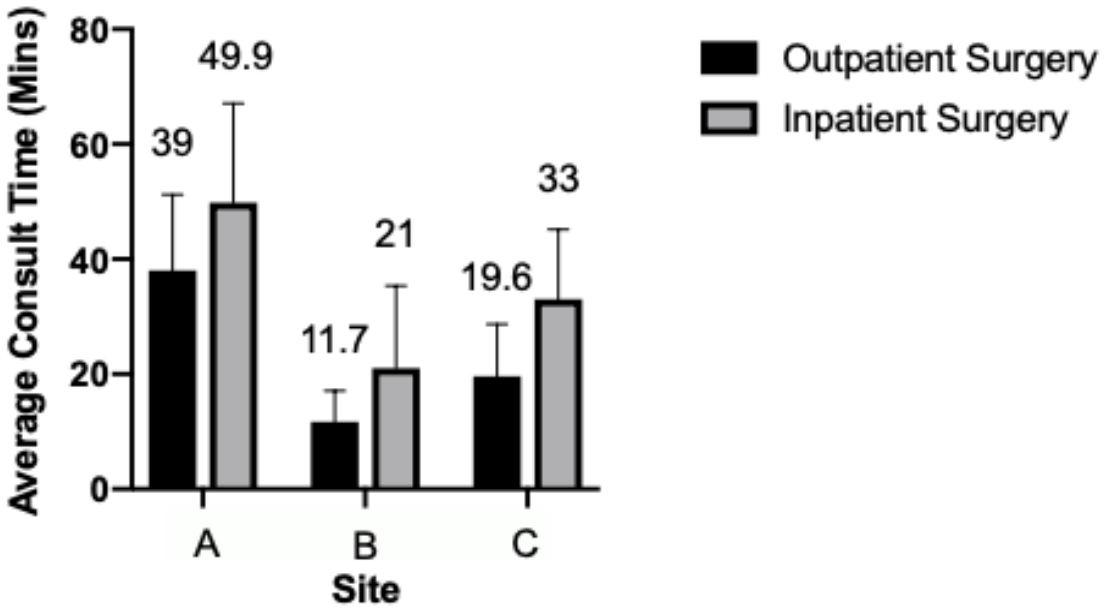


Figure 1. Consult Times for In-Patient Surgery & Out-Patient Surgery at Each Site.

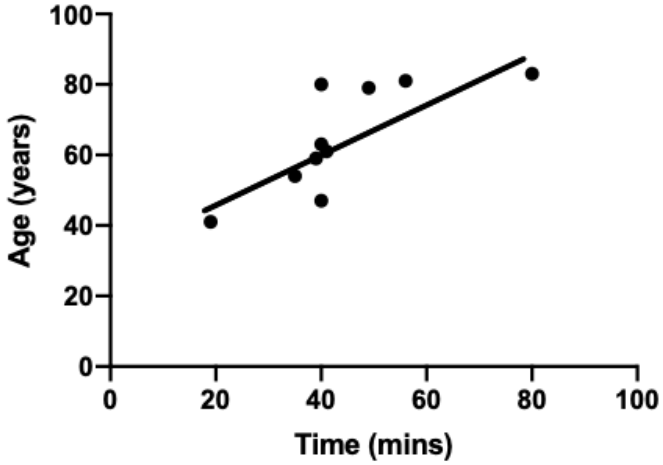


Figure 2. Site A Correlation Between Patient Age and Consult Time. There is a strong correlation between patient age and nursing consult time (r = 0.77).

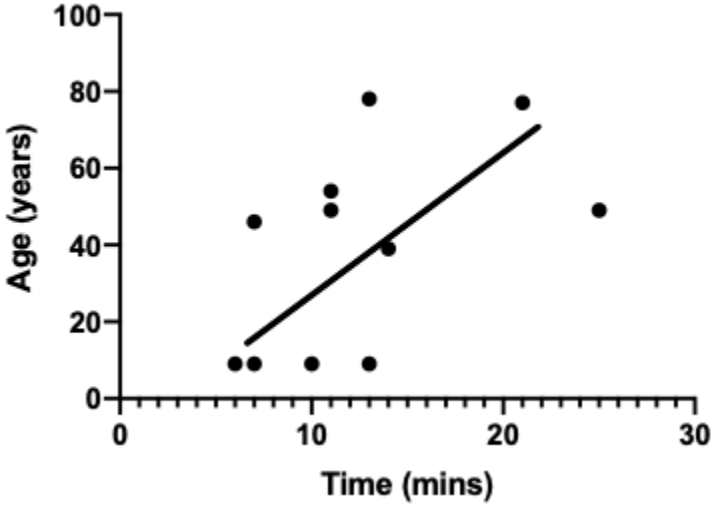


Figure 3. Site B Correlation Between Patient Age and Consult Time**.** There is a moderate correlation between patient age and nursing consult time (r = 0.52).

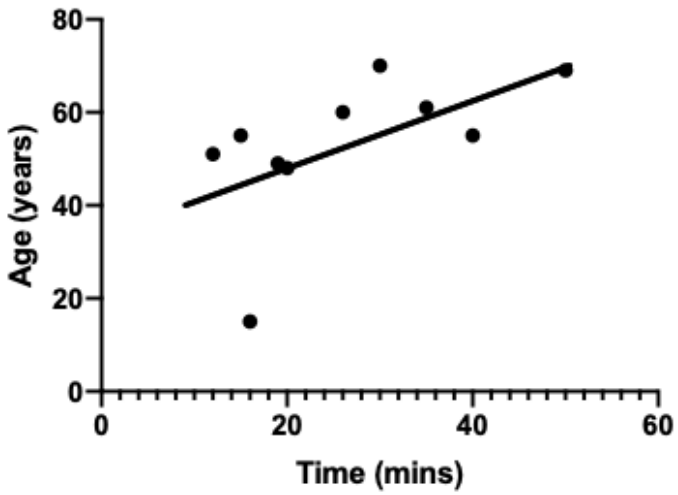


Figure 4. Site C Correlation Between Patient Age and Consult Time**.** There is a moderate correlation between patient age and nursing consult time (r = 0.58).

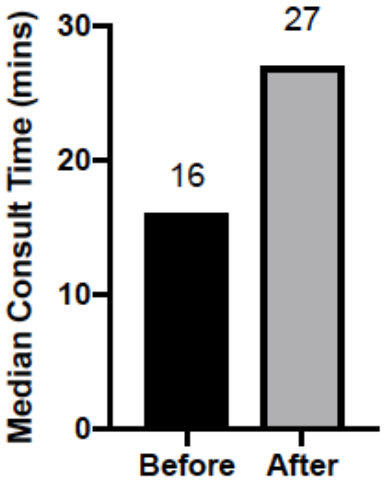


Figure 5. Day-surgery consult times before and after new nursing assessment form implementation at site C**.** The difference in median consult time before and after the implementation of the new assessment form was not statistically significant (P>0.05). Before n=5; after n=6.

Discussion

The purpose of this study was to use the PDSA process in order to 1) identify areas of potential standardization in the PAC, 2) identify any possible interventions, 3) Assess the overall feasibility of standardization. Using observational assessments, process mapping, and holding a focus group, it was identified that the most feasible way to begin the standardization of the pre-

operative process was to focus on standardizing nursing consults within the pre-operative assessment clinics.

Through the PDSA process the use of a standardized assessment form was identified as a potential intervention to increase overall standardization in PAC. Following consultation with stakeholders it was implemented in three PACs. Analysis of the form showed that at site C the new form was found to have no significant impact on the consult time and required change management interventions such as utilizing nurse educators to assist with the transition (Figure 5). Although nursing feedback was considered before the implementation of the form, it was not until the form was utilized in the context of the clinic that significant changes and areas for improvement were identified. A barrier to satisfaction and implementation of the new form at site B included a turnover in staff, including a nurse working in the clinic who was just becoming familiar with the pre-operative process and undergoing training in their new role. It was noted by the staff that the form was much less comprehensive than its predecessors, which prompted the nurses to revert back to utilizing old forms as a precaution to ensure that sufficient patient information was collected during the consult. What emerged from this finding was that including a pilot trial phase before implementation of subsequent forms would allow nurses to provide more comprehensive feedback by identifying problem areas earlier in the process, with the goal of having them feel more confident utilizing it in the clinic.

What emerged from this study was the importance of placing emphasis on gathering feedback from frontline staff, in order to come up with an appropriate course of action for the short term (Appendix 1). When implementing QI projects within a complex adaptive system, it is crucial to focus on interventions that are relevant and feasible for all hospital sites within the system and to gain a comprehensive understanding of the environment and culture in which these interventions will be implemented through co-design.

It is recommended that future renditions of a standardized patient assessment form be created using a co-design thinking framework, where nurses, nurse educators, and front-line staff are directly involved with its creation rather than having a quality improvement team develop it and ask for their feedback and approval. This process would be more efficient and would increase satisfaction and buy-in, by prioritizing deep empathy for end-user desires, needs, and challenges, while fully understanding the problems with the form in order to develop more comprehensive and effective solutions from the beginning (7,8).

The results of the root cause analysis in PDSA cycle 1 (e.g., identifying standardization issues) reinforce that there are substantial structural and organizational differences between each site's PAC. While a potential intervention—standardized assessment forms—was identified, factors that posed a greater challenge for intervention, such as variability in patient cases, different technology, the varying number of clinic staff, and the physical architectural differences of each PAC were all found to contribute to the lack of standardization. To standardize the differences in technology, staffing, and physical elements at each PAC, significant investments in capital and human resources are required. These are factors beyond the scope of this project and do not warrant the utilization of rapid PDSA cycle methodology.

The variability in patient cases, which was quantified using patient age and type of surgery in this study (Figure 1-4), also posed a difficult challenge to standardizing consult times. Due to the varying ages of patients that attended each clinic, consult times were highly variable. Figures 2-4 suggest that older patients required longer consultation times, which is especially relevant to NH due to the aging population in Niagara. Figure 1 suggests that out-patient surgery consults require less time than in-patient consults. This could further assist pre-op clinics in allocating appropriate amounts of time to each appointment to streamline the standardization process. Addressing this issue was beyond the scope of this paper, however, further research should focus on the impact of patient cases on consultation time by quantifying the number of additional co-morbidities, type of procedure and health-literacy levels, and their effect on consult time.

The Choosing Wisely Canada guidelines provide a framework for standardizing the pre-operative process, which is important in increasing efficiency and decreasing wait times. In the context of NH, the first step to implementing the Choosing Wisely Canada guidelines is to assess the pre-operative clinics. This project accomplished that objective by including an assessment of necessary changes based on staff feedback at each site. By gathering specific recommendations that are targeted and sensitive to the local environment at each site, credibility and buy-in for this pre-op assessment style can be achieved (3). This study identified many barriers to implementing standardization of pre-op assessments, many of which would be expensive to address and are therefore not feasible. However, one possible initiative that was not addressed here was the extreme variability seen in the clinic, due to individual factors. While we have recommended that this be investigated in future studies, it would also be a possible area of application of the Clinical Decision Tool. This toolkit provided by the Choosing Wisely Canada guidelines would allow surgeons to identify patients requiring a pre-op clinic visit based on pre-determined indicators such as patient physiological status, and surgical category (3). The adoption of these guidelines is predicted to eliminate the extreme case-mix and reduce the large amount of variability seen in the pre-op clinic (3).

The research conducted through this project connects directly with Institute for Healthcare Improvement's New Rules for Radical Redesign in Health Care (9). For future standardization projects with a focus on pre-operative assessment clinics, the specific rules that should be the core of the project are: collaborate and cooperate; standardize what makes sense; and move knowledge not people (9). Thus, the process of standardization must begin with collaboration and cooperation through co-design with pre-op clinic staff, followed by identifying elements of the complex adaptive system that can feasibly be standardized to reduce unnecessary variation. A larger scale PAC standardization will require utilization of modern digital care, such as an electronic patient pre-op record (10), and adoption of Choosing Wisely Canada's guideline to eliminate unnecessary pre-op visits. By focusing on these elements, the standardization process can take place more efficiently and effectively, especially across a complex adaptive system where there are many key stakeholders who play a crucial role at all stages of the process,

rather than onboarding the frontline staff into the project after the creation and identification of the QI initiative.

A limitation of PDSA cycles is that the resources, skills and expertise that they require are often significantly underestimated, which can hinder their success (11). This was apparent when trialing the new form, as the nursing staff were required to devote additional time to learn the new form and provide feedback on what should be changed. In a clinical setting where the patient is their main priority it is recognized that concurrent engagement in the "Study" phase of the PDSA cycle may be a competing priority, which in turn can reduce buy-in and willingness to engage in the intervention.

Conclusions

By using PDSA cycles to assess the feasibility of implementing a standardized pre-operative process across a hospital system, it was evident that there is a need to evaluate the factors that affect the case-mix of patients that attend the pre-operative assessment clinic. Patient age, complexity of their scheduled surgery, and additional co-morbidities are all factors that affect the course of action that is to be taken to prepare the patient for their surgery, as well as the time it takes to conduct the pre-operative consults. Given the extreme case-mix of patients, varying staff resources, and differences in technology at each hospital site, it was not feasible for us to implement a standardized nursing assessment process. These findings support the future implementation of Choosing Wisely Canada guidelines to reduce unnecessary pre-operative visits, which in turn will reduce the case-mix of patients, allowing for feasible system-wide standardization. Furthermore, this research highlights the strong need for a co-design framework to be used in the identification and planning phases of the standardization process. To implement a standardized pre-operative assessment process at a system level, it is crucial that key stakeholders from each hospital site, such as frontline staff, are engaged in all stages of the process.

Acknowledgements

We would like to thank the pre-operative clinics and associated staff within the Niagara Health System for their support in the undertaking of this project.

References

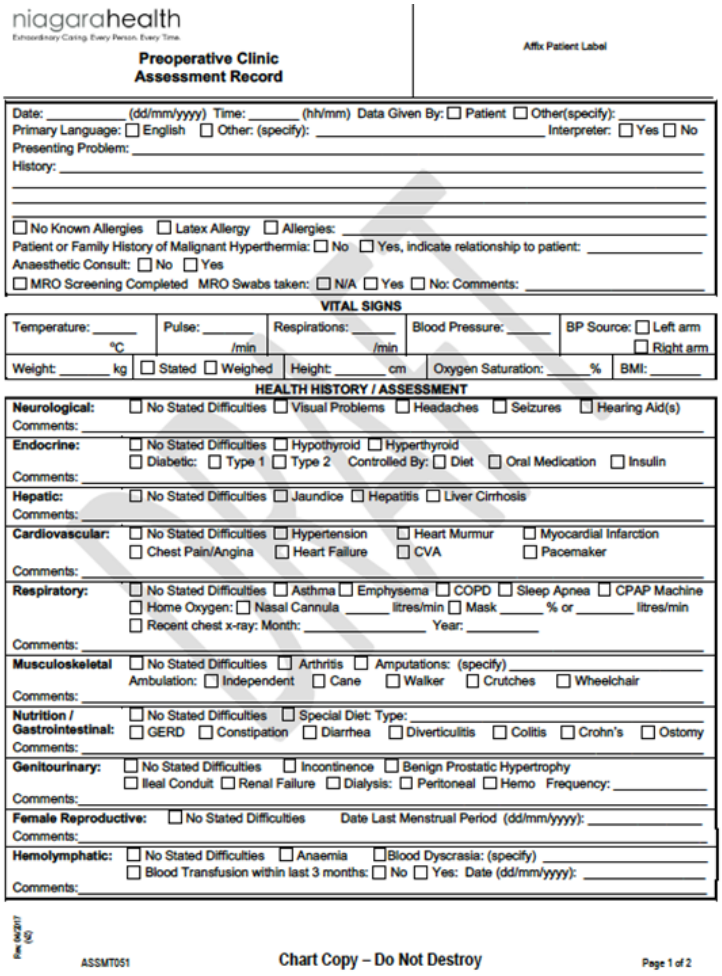
1. Stausberg J, Koch D, Ingenerf J, Betzler M. Comparing paper-based with electronic patient records: lessons learned during a study on diagnosis and procedure codes. Journal of the American Medical Informatics Association. 2003 Sep 1;10(5):470-7..
2. Ausset S, Bouaziz H, Brosseau M, Kinirons B, Benhamou D. Improvement of information gained from the pre-anaesthetic visit through a quality-assurance programme. British

journal of anaesthesia. 2002 Feb 1;88(2):280-3..
3. Choosing Wisely Canada. Drop the Pre-Op: A toolkit for reducing unnecessary visits and investigations in pre-operative clinics. [Internet]. 2017 [Cited 2017 Nov 27]. Available from: https://choosingwiselycanada.org/perspective/preop-toolkit/
4. Powell AE, Rushmer RK, Davies HT. A systematic narrative review of quality improvement models in health care. NHS Quality Improvement Scotland; 2009 Feb 1..
5. Taylor MJ, McNicholas C, Nicolay C, Darzi A, Bell D, Reed JE. Systematic review of the application of the plan–do–study–act method to improve quality in healthcare. BMJ Qual Saf. 2014 Apr 1;23(4):290-8.
6. Given LM, editor. The Sage encyclopedia of qualitative research methods. Sage publications; 2008 Aug 19. 812.
7. Langley GJ, Moen RD, Nolan KM, Nolan TW, Norman CL, Provost LP. The improvement guide: a practical approach to enhancing organizational performance. John Wiley & Sons; 2009 Jun 3.
8. Seidel VP, Fixson SK. Adopting design thinking in novice multidisciplinary teams: The application and limits of design methods and reflexive practices. Journal of Product Innovation Management. 2013 Dec;30:19-33.
9. Roberts JP, Fisher TR, Trowbridge MJ, Bent C. A design thinking framework for healthcare management and innovation. InHealthcare 2016 Mar 1 (Vol. 4, No. 1, pp. 11-14). Elsevier.
10. Loehrer S, Feeley D, Berwick D. 10 New Rules to Accelerate Healthcare Redesign. Bold aspirations to guide healthcare organizations during an era of reform. Healthcare executive. 2015;30(6):66-8.
11. Bouamrane MM, Mair FS. Implementation of an integrated preoperative care pathway and regional electronic clinical portal for preoperative assessment. BMC medical informatics and decision making. 2014 Dec;14(1):93.

Appendix

Pre-Op Clinic Staff Feedback	Long Term Changes	Short Term Changes
• There is a great deal to cover in a short amount of time • Volume of paperwork results in consults taking more time than scheduled • Patient population has an impact on consult time • Best Possible Medication History (BPMH) filled out electronically would be more efficient • Patients with more co-morbidities require more time • Seniors require more time • Varied information is provided to patients by surgeons • Collecting a proper medication history is very time consuming • For mandatory pre-op at site B, it would require another clerk and another nurse	• Electronic and printable BPMH • Mandating pre-op for all patients • Increased frequency of anesthesia presence in the clinic	• Computerization of patient history and an updated computer system • Update the patient history form in Meditech • Standardization of admission history forms

Appendix 1. Qualitative Feedback from Pre-Operative Clinic Staff. Comments collected during the observational visits that took place at Pre-Operative Assessment Clinics across NH. Long Term Changes and Short Term Changes were identified by staff at a focus group and were used to guide future interventions intended to standardize the pre-operative process across NH.



niagarahealth
Extraordinary Caring. Every Person. Every Time.

Preoperative Clinic Assessment Record

Affix Patient Label

Date: _____ (dd/mm/yyyy) Time: _____ (hh/mm) Data Given By: ☐ Patient ☐ Other(specify): _____
Primary Language: ☐ English ☐ Other: (specify): _____ Interpreter: ☐ Yes ☐ No
Presenting Problem: _____
History: _____

☐ No Known Allergies ☐ Latex Allergy ☐ Allergies: _____
Patient or Family History of Malignant Hyperthermia: ☐ No ☐ Yes, indicate relationship to patient: _____
Anaesthetic Consult: ☐ No ☐ Yes
☐ MRO Screening Completed MRO Swabs taken: ☐ N/A ☐ Yes ☐ No: Comments: _____

VITAL SIGNS

Temperature: _____ °C	Pulse: _____ /min	Respirations: _____ /min	Blood Pressure: _____	BP Source: ☐ Left arm ☐ Right arm
Weight: _____ kg ☐ Stated ☐ Weighed	Height: _____ cm	Oxygen Saturation: _____ %	BMI: _____	

HEALTH HISTORY / ASSESSMENT

Neurological: ☐ No Stated Difficulties ☐ Visual Problems ☐ Headaches ☐ Seizures ☐ Hearing Aid(s)
Comments: _____

Endocrine: ☐ No Stated Difficulties ☐ Hypothyroid ☐ Hyperthyroid
☐ Diabetic: ☐ Type 1 ☐ Type 2 Controlled By: ☐ Diet ☐ Oral Medication ☐ Insulin
Comments: _____

Hepatic: ☐ No Stated Difficulties ☐ Jaundice ☐ Hepatitis ☐ Liver Cirrhosis
Comments: _____

Cardiovascular: ☐ No Stated Difficulties ☐ Hypertension ☐ Heart Murmur ☐ Myocardial Infarction
☐ Chest Pain/Angina ☐ Heart Failure ☐ CVA ☐ Pacemaker
Comments: _____

Respiratory: ☐ No Stated Difficulties ☐ Asthma ☐ Emphysema ☐ COPD ☐ Sleep Apnea ☐ CPAP Machine
☐ Home Oxygen: ☐ Nasal Cannula _____ litres/min ☐ Mask _____ % or _____ litres/min
☐ Recent chest x-ray: Month: _____ Year: _____
Comments: _____

Musculoskeletal ☐ No Stated Difficulties ☐ Arthritis ☐ Amputations: (specify) _____
Ambulation: ☐ Independent ☐ Cane ☐ Walker ☐ Crutches ☐ Wheelchair
Comments: _____

Nutrition / Gastrointestinal: ☐ No Stated Difficulties ☐ Special Diet: Type: _____
☐ GERD ☐ Constipation ☐ Diarrhea ☐ Diverticulitis ☐ Colitis ☐ Crohn's ☐ Ostomy
Comments: _____

Genitourinary: ☐ No Stated Difficulties ☐ Incontinence ☐ Benign Prostatic Hypertrophy
☐ Ileal Conduit ☐ Renal Failure ☐ Dialysis: ☐ Peritoneal ☐ Hemo Frequency: _____
Comments: _____

Female Reproductive: ☐ No Stated Difficulties Date Last Menstrual Period (dd/mm/yyyy): _____
Comments: _____

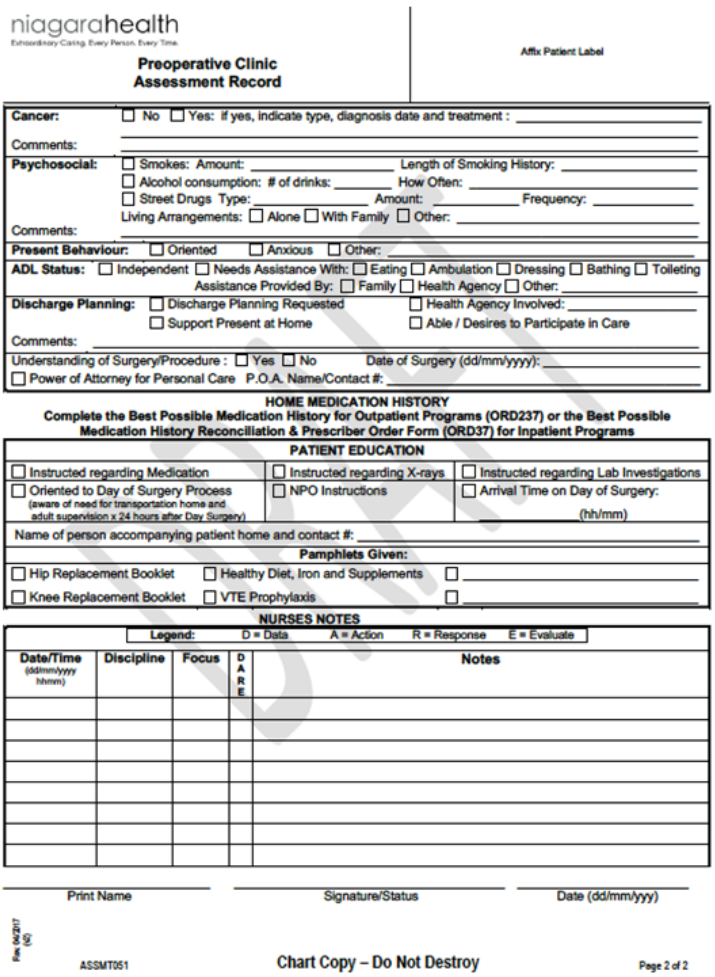
Hemolymphatic: ☐ No Stated Difficulties ☐ Anaemia ☐ Blood Dyscrasia: (specify) _____
☐ Blood Transfusion within last 3 months: ☐ No ☐ Yes: Date (dd/mm/yyyy): _____
Comments: _____

Rev 04/2017 (4)

ASSMT051

Chart Copy – Do Not Destroy

Page 1 of 2



niagarahealth
Extraordinary Caring. Every Person. Every Time.

Preoperative Clinic Assessment Record

Affix Patient Label

Cancer: ☐ No ☐ Yes: If yes, indicate type, diagnosis date and treatment : _____
Comments: _____

Psychosocial: ☐ Smokes: Amount: _____ Length of Smoking History: _____
☐ Alcohol consumption: # of drinks: _____ How Often: _____
☐ Street Drugs Type: _____ Amount: _____ Frequency: _____
Living Arrangements: ☐ Alone ☐ With Family ☐ Other: _____
Comments: _____

Present Behaviour: ☐ Oriented ☐ Anxious ☐ Other: _____

ADL Status: ☐ Independent ☐ Needs Assistance With: ☐ Eating ☐ Ambulation ☐ Dressing ☐ Bathing ☐ Toileting
Assistance Provided By: ☐ Family ☐ Health Agency ☐ Other: _____

Discharge Planning: ☐ Discharge Planning Requested ☐ Health Agency Involved: _____
☐ Support Present at Home ☐ Able / Desires to Participate in Care
Comments: _____

Understanding of Surgery/Procedure : ☐ Yes ☐ No Date of Surgery (dd/mm/yyyy): _____
☐ Power of Attorney for Personal Care P.O.A. Name/Contact #: _____

HOME MEDICATION HISTORY
Complete the Best Possible Medication History for Outpatient Programs (ORD237) or the Best Possible Medication History Reconciliation & Prescriber Order Form (ORD37) for Inpatient Programs

PATIENT EDUCATION

☐ Instructed regarding Medication	☐ Instructed regarding X-rays	☐ Instructed regarding Lab Investigations
☐ Oriented to Day of Surgery Process (aware of need for transportation home and adult supervision x 24 hours after Day Surgery)	☐ NPO Instructions	☐ Arrival Time on Day of Surgery: _____ (hh/mm)

Name of person accompanying patient home and contact #: _____

Pamphlets Given:

☐ Hip Replacement Booklet	☐ Healthy Diet, Iron and Supplements	☐ _____
☐ Knee Replacement Booklet	☐ VTE Prophylaxis	☐ _____

NURSES NOTES

Legend: D = Data A = Action R = Response E = Evaluate

Date/Time (dd/mm/yyyy hh/mm)	Discipline	Focus	D A R E	Notes

Print Name _____ Signature/Status _____ Date (dd/mm/yyyy) _____

Rev 04/2017 (4)

ASSMT051

Chart Copy – Do Not Destroy

Page 2 of 2

Appendix 2. Standardized Nursing Assessment Form.

Original Research Article

Do socioeconomic factors and primary care model affect early breast cancer diagnosis in a cohort of breast cancer patients in an urban Canadian centre?

Jennifer Li MD[a], Sylvie D. Cornacchi MSc[a], Forough Farrokyar PhD[a,d], Shawn Forbes MD, MSc[a,b], Susan Reid MD[a,b], Nicole Hodgson MD, MSc[a,b], Sarah Lovrics BA[a], Kristen Lucibello MSc[a], and Peter Lovrics MD[a,b,c]

[a]Department of Surgery, McMaster University, Hamilton, ON, Canada

[b]Department of Surgical Oncology, Hamilton Health Sciences and Juravinski Hospital and Cancer Centre, Hamilton, ON

[c]Department of Surgery, St. Joseph's Healthcare, Hamilton, ON

[d]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON

Abstract

Objectives: Studies have shown an association between socioeconomic status (SES) and breast cancer (BC) treatment and diagnosis. We examined the relationship between SES, primary care physician (PCP) model and early detection of BC, as defined by asymptomatic screening and early stage at diagnosis, in a universal healthcare system.

Methods: Data were collected for consecutive patients diagnosed with BC from January 2010 to December 2011.Variables included patient and disease factors, type of PCP, stage at diagnosis and method of tumour identification. Area-level SES variables were obtained from 2006 Canadian census data. Multivariable logistic regression was used to identify predictors of early BC diagnosis. Odds ratios with 95% confidence intervals were reported.

Results: Results: A total of 721 patients were treated for breast cancer during the 2-year period. Predictors of early diagnosis through screening included: patients aged 51-70 (OR 4.3, 95% CI:2.6-7.2), BMI > 30 (1.5, 1.0-2.3), not employed (0.5, 0.3-0.8), and previous screening within 2 years (3.0, 2.0-4.4). Predictors of diagnosis at an early stage were having a 1st degree relative with breast cancer (2.2, 1.3-3.8) and having screening at an Ontario Breast Screening Program (2.9, 1.6-5.2).

Conclusion: Certain patient variables such as age and family history, predicted the likelihood of early detection of BC by asymptomatic screening and diagnosis at an early stage. In our urban cohort of BC patients, SES factors were not found to be predictors of early detection of BC.

Keywords: income quintiles; education; stage at diagnosis; screening; family practitioner; breast cancer

Corresponding author: Peter Lovrics, lovricsp@mcmaster.ca

Introduction

Breast cancer is the most commonly diagnosed type of cancer in women with 26,3000 new cases diagnosed in Canada in 2017[1]. It is also the second most common cause of cancer mortality in Canadian women, accounting for 13% of all cancer deaths[1]. Breast cancer is frequently diagnosed by screening mammography, as per the current Cancer Care Ontario (a provincial government agency created to drive quality and continuous improvement in cancer prevention and screening) guideline recommendations for women starting at age 50.[2,3] Breast cancer is treated with a multidisciplinary approach involving surgery, radiation, chemotherapy, and hormonal treatments. With advances in treatment, it is a highly curable cancer if diagnosed at an early stage[2,3].

There is growing evidence that non-biological factors may have an impact on the detection, treatment, and outcome of breast cancer in women. Many studies have shown a positive relationship with higher socioeconomic status (SES) associated with improved breast cancer survival in the United Kindgom (UK)[4], United States (US)[5-8], the Netherlands[9], Australia[10,] and Canada.[11-14] In addition, women with lower SES in Canada and the US were found to participate less often in screening programs,[15-17] to receive adjuvant chemoradiation less often[18-20], and were more likely to be diagnosed with breast cancer at a later stage than women with higher SES.[21] In Ontario, participation in cancer screening has been found to be lower in women with less education, lower SES, recent immigrant status, and those living in rural areas.[22-25] Furthermore, some studies have suggested that the model of healthcare delivery (universal healthcare vs. private or mixed healthcare) may also affect outcomes [26,27.] A systematic review by Gorey[26] found that in the lowest income areas, Canadian women had a significant five-year survival advantage over women in the US in various metropolitan and urban areas. They also found that US women less than 65 years of age who were not yet Medicare eligible were even more disadvantaged than Canadian women the same age. The authors suggest that the lack of healthcare insurance and consequent lack of access to health care services in the US compared to Canada explained their results.[26,27]

Breast cancer and primary care

In Ontario, Canada, the primary care provider (PCP) is the gate keeper to healthcare who initiates the process of referral to surgeons or oncologists for patients with breast cancer. Women are most frequently diagnosed with breast cancer after presentation to their PCP with a symptomatic lesion, or through a screening procedure.[28] Patients without a PCP may present with breast symptoms to a walk-in clinic or emergency room. Screening can be arranged by a PCP, either by referral to the Ontario Breast Screening Program (OBSP) or by imaging requested by one's PCP. While the OBSP can also be accessed by self-referral (OBSP invites screen-eligible patients by mail to book screening appointments), PCPs are encouraged to inform eligible patients about the program and play a key role in the diagnosis of breast cancer.[29] Some PCP characteristics such as identifying as male, physicians not working in a patient enrollment PCP model, and international

medical graduate PCPs in Ontario have been associated with lower rates of cancer screening.[24,28] Esteva et al.[30] found that recommendations from physicians increase participation in public breast screening programs, while Sudtradhar et al.[29] found that visiting a PCP was associated with a significant increase in the uptake of periodic mammograms in an Ontario cohort. Additionally, decreased PCP availability has been shown to be a contributing factor to lower breast cancer survival in some jurisdictions.[31] The Ontario Medical Association (OMA) has estimated that 927,000 residents in Ontario did not have a PCP in 2012, with a shortage of 1000 physicians, potentially affecting breast cancer detection and management.[32]

Primary care models in Ontario

There are currently several models of primary care in Ontario with differing characteristics, including whether they are solo or group practices, associated with allied health, and the type of monetary compensation received including salaried physicians, "fee-for-service" payments (FFS), enhanced fee-for-service (EFFS), or various blended capitation payments (ie., fixed, pre-arranged payments for each patient enrolled within a PCP's practice not linked to specific service visits).[33-36] The different PCP models include: Community Health Centres (CHC), Fee for Service (FFS), Family Health Groups (FHG), Comprehensive Care Model (CCM), Family Health Organizations (FHO), and Family Health Networks (FHN) that may or may not include a Family Health Team (FHT) (e.g., FHO or FHN with Allied Family Health Team).[33-36] The different PCP models and their characteristics are outlined in Table 1. There is a smaller group of "other" models that are isolated to small rural areas, and a group with no PCP. Glazier et al,[36-38] found that FFS and EFFS models served patients that were predominantly urban, with a higher proportion of recent immigrants, lower income and patients with higher levels of comorbidity and expected resource use compared to FHO and FHO-FHT models. They also found that FHO-FHT had higher colorectal and cervical cancer screening rates compared to FFS and EFFS models[36-38]. We are not aware of studies examining the relationship between the type of PCP and breast cancer diagnosis and stage at presentation.

SES and breast cancer incidence/mortality in Hamilton, Ontario

The relationship between SES and numerous health parameters and longevity have been studied in Hamilton, Ontario.[39] The city of Hamilton is a midsize industrial city with a population of 505,000 residents and is an amalgamation of five generally affluent suburban communities and a central urban area with a lower-income downtown area.[39] Breast cancer incidence in the inner-city core of Hamilton was 3.5% lower than in five more affluent suburbs in Hamilton, but the breast cancer mortality rate was 7% higher.[40] In light of this study, we hypothesize that SES factors may contribute to the early detection of breast cancer, even in a universal healthcare system. There are currently more than 345 PCPs practicing in the Hamilton region (2017 data),

Table 1. Primary Care Physician Models in Ontario[33-36]

Remuneration	Primary Care Physician (PCP) Model	PCP model characteristics
Salaried models	Community Health Centre (CHC)	• Interdisciplinary teams serve hard to serve communities
Fee for Service (FFS)	Fee for Service (FFS)	• Very few provide comprehensive care • Do not roster patients, no after hour requirements
Enhanced FFS-based blended models (EFFS)	Family Health Group (FHG)	• Primarily fee-for-service • Practice in a group with incentive for preventative care • Must provide after hour availability • Some groups enroll patients
	Comprehensive care model (CCM)	• Solo PCPs with same characteristics as FHG
Capitation based blended models without Allied Health Team	Family Health Organizations (FHO)	• Practice in a group with incentive for preventative care • Must provide after hour availability • Patient rostering/enrolment
	Family Health Networks (FHN)	
Capitation based blended model with Allied Family Health Team (FHT)	Family Health Organizations (FHO-FHT)	• Practice in a group with incentive for preventative care • Must provide after hour availability • Patient rostering/enrolment • Funding available for allied health professionals and overhead associated with it (eg. nurse practitioners, dieticians, social workers)
	Family Health Networks (FHN-FHT)	

within various PCP models.[41,34] It is possible that some aspects of the detection and management of breast cancer may vary with PCP models (e.g., monetary incentives for cancer screening in some PCP models may encourage PCPs to more actively recommend screening tests) or that different PCP models might attract different patient populations, which in turn could affect early detection of breast cancer.[36,42]

Past studies have suggested SES influences the rate of BC screening. The first objective of this study is to assess whether SES predicts asymptomatic screening and early stage at diagnosis in a universal healthcare setting. Secondly, no previous studies have assessed the correlation between type of PCP and BC diagnosis. Our study is the first to investigate the relationship between PCP and breast cancer diagnosis in the Hamilton region.

Materials and methods

Study cohort and data collection

A retrospective chart review of consecutive patients diagnosed with breast cancer (surgical and non-surgical cases) living in Hamilton, Ontario was conducted over a two year period (January 2010 to December 2011). Cases were identified through health records queries using Canadian Classification of Health Interventions (CCI) codes for breast cancer surgical procedures (ICES Atlas Appendix[43]) and ICD-9 and ICD-10 Diagnosis codes (for invasive and DCIS) for day surgery and inpatient charts from hospital databases. Newly diagnosed breast cancer cases were also identified in the Regional Cancer Centre database to ensure all cases were identified (duplicates were excluded). Breast cancer included invasive disease and ductal cancer in situ. Male patients, duplicate charts, those diagnosed with benign breast disease, and patients who reside outside of Hamilton or had their primary treatment for breast cancer outside Hamilton were excluded. Local Research Ethics Board approval was obtained (REB #14-193-C). Trained data abstractors performed chart review from hospital and cancer centre charts to extract data on patient and disease characteristics. Patient demographics included age at diagnosis, marital status, obesity, and body mass index BMI > 30. Employment status was defined as employed, not employed (includes those on disability and homemakers), or retired. Data on smoking status, comorbidities, 1st degree relative with breast cancer, method of tumor identification (asymptomatic screening vs. symptomatic), location of primary imaging (Ontario Breast Screening Program (OBSP), hospital or non-hospital clinic), and disease stage at diagnosis were also collected.

Primary care physician model

The name of each patient's PCP was identified from the hospital chart. A College of Physicians and Surgeons of Ontario (CPSO) search (http://www.cpso.on.ca/Public-Register/All-Doctors-Search) was used to identify the number of years of practice, gender, and hospital privileges of each PCP. PCP model under which each PCP practiced was obtained from the Hamilton Physicians Primary Care Physician Database and included the following groups: FFS, EFFS FHO, and FHO-FHT.

Census data

Patients' postal codes were linked to the 2006 Canadian Census data to extract the following variables: immigration status (% immigrant last five years), education level (% completing college or university), and average income of the census tract of patient residence. Income was divided into quintiles.

Statistical analyses

Categorical variables were reported as counts and percentages and compared using Chi square or Fisher's exact test. Continuous variables were reported as mean with standard deviation (SD) and compared using t test for independent samples. Multivariable logistic regression analysis was performed to identify which variables (patient, SES, PCP model) had an impact on method of tumour identification and stage at diagnosis. Odds ratios (OR) with the corresponding 95% confidence intervals and Hosmer-Lemeshow goodness-of-fit values were calculated. Multicollinearity was checked using correlation analysis. To maximize power, univariable analysis was performed and variables with value less than 0.1 were entered into the multivariable regression. A p-value of 0.05 was considered for statistical significance. Data analyses were performed using SPSS Statistical Software Version 25.0 (IBM, New York, NY).

Results

Health records queries identified 1057 consecutive breast cancer surgical cases between January 2010 and December 2011 that were reviewed. Of these, 649 cases met inclusion criteria. An additional 72 breast cancer cases were identified (non-surgical and neo-adjuvant therapy cases) by cross-referencing with the Regional Cancer Centre database. Full data were abstracted from these 721 breast cancer cases (Figure 1). Table 2 outlines demographic, area-level SES, and breast cancer characteristics of the study cohort. Of note, there was a relatively even distribution of income quintiles, and a relatively even split of diagnosis by screening or symptomatic disease (47% vs 53%).

Ninety-eight percent of patients in our cohort had a PCP. Of the 11 (1.5%) patients without a PCP, 90% had their tumour identified by symptomatic presentation compared to 53% of patients with a PCP, and 55% were stage 3-4 compared to 24% of those with a PCP ($p<0.01$, data not shown). Sixty-four percent of PCPs were male, 41% had an academic appointment, and 79% had hospital privileges. Seventeen percent had

Figure 1: Study Cohort

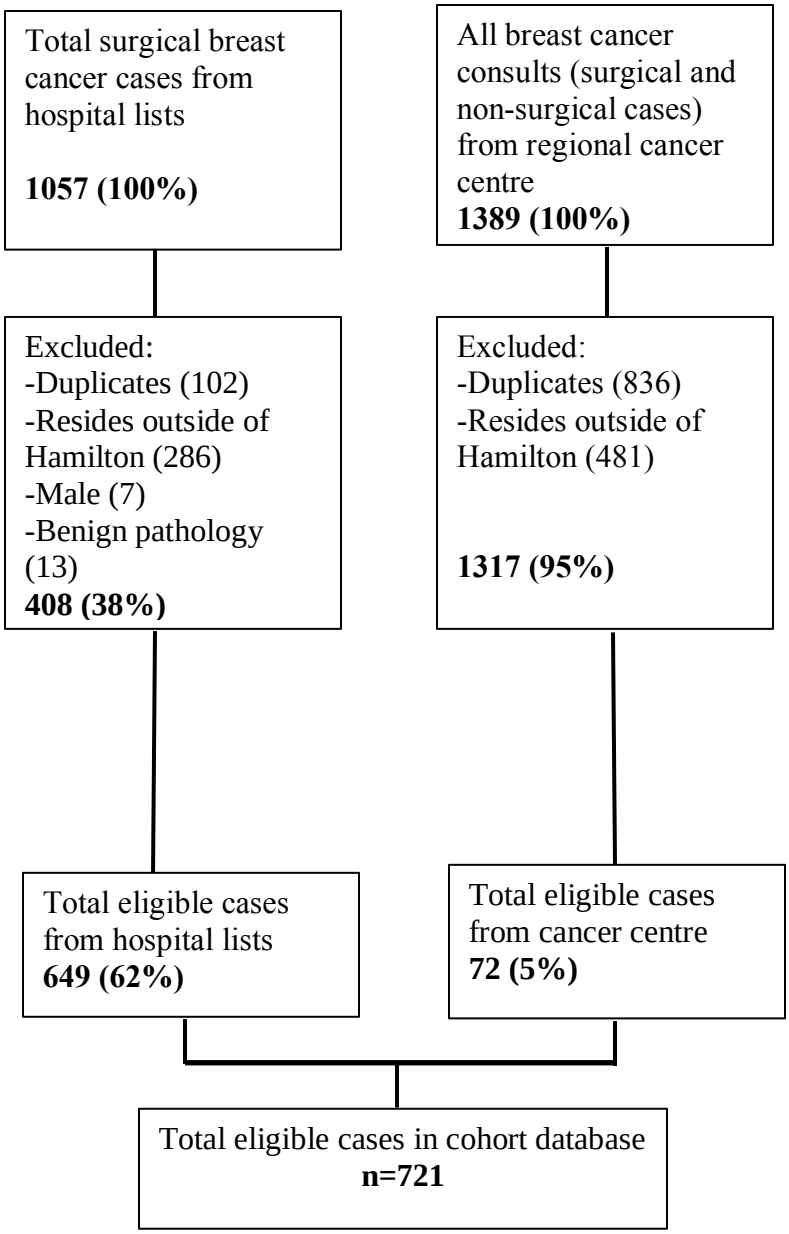


Table 2. Patient, socioeconomic factors, disease status and type of surgery for breast cancer cohort.

Variable	n=721	%
Age at diagnosis		
≤ 50 years	149	21
51 – 70 years	364	50
> 70 years	208	29
Obese (BMI > 30)		
Yes	255	35
No	435	61
NOS	31	4
Employment		
Employed	277	38
Not employed	151	21
Retired	279	39
NOS	14	2
Marital Status		
Married	447	62
Not married	272	38
NOS	2	0.3
First Degree Relative with BC		
Yes	159	22
No	519	72
NOS	43	6
Smoking History		
Smoker or previous smoker	289	40
Never smoked	426	59
NOS	6	1
Comorbidities		
None	183	25
1 or more	538	75
Income Quintiles		
1 (lowest)	147	20
2	141	20
3	148	21
4	140	19
5 (highest)	139	19
% neighborhood pursuing post-secondary education		
>40%	304	42
31-40%	237	33
< 31%	177	25
% neighborhood who are new immigrants		
> 30%	199	28
21-30%	224	31

< 20%	295	41
Method Tumour Identification		
Asymptomatic Screening	337	47
Symptomatic work-up	383	53
Location Primary Imaging		
OBSP	258	36
Hospital	314	44
Non-hospital Clinic	140	19
NOS	9	1
Imaging in past 2 years		
Yes	317	44
No	313	43
NOS	91	13
Previous Breast Cancer		
Yes	87	12
No	634	88
Recurrent Breast Cancer		
Yes	50	7
No	671	93
Disease Stage (TNM)		
Stage 0 & 1	323	45
Stage 2	222	31
Stage 3 & 4	176	24

BC – breast cancer; NOS – not otherwise specified/missing; BMI – body mass index; OBSP – Ontario Breast Screening Program; Comorbidities included were chronic obstructive pulmonary disease, rheumatic disease, coronary artery disease, myocardial infarction, coronary heart failure, diabetes, kidney disease, major psychiatric illness, morbid obesity (BMI >40), other cancer diagnosis, osteoporosis, hypertension, hypercholesterolemia, and neurodegenerative diseases (e.g. Parkinson's disease).

been in practice 10 years or less, 21% had practiced for 11-20 years, 28% had practiced for 21-30 years, and 33% had been in practice more than 30 years. The majority of PCPs worked in a FHO-FHT (64%) compared to 15% in a FHO and 17% in FFS/EFFS

Table 3 shows the univariate analysis for the method of cancer identification, stage at diagnosis, and patient characteristics for each type of PCP model. The method of diagnosis and stage at diagnosis, as well as most patient characteristics, did not vary with the PCP type. However, differences were found between PCP models for immigrant status, education, income quintile, employment status, and location of imaging ($p<0.05$). The FFS model had more patients living in neighbourhoods with a higher percentage of immigrants, lower percentage with post-secondary education, more women who were not employed and in the lowest income quintile than capitation-based models. FFS also had more patients who had their breast cancer diagnosed by imaging performed at a non-hospital clinic and fewer through an OBSP site.

Table 4 presents the univariate analysis of area-level SES and method of tumour identification and stage at diagnosis. Breast cancer was more often identified by asymptomatic

Table 3. Primary Care Physician Model by outcomes and SES variables.

Variable	Primary Care Physician Model				
	FFS (n=49) n (%)	EFFS (n=72) n (%)	FHO (n=106) n (%)	FHO-FHT (n=463) n (%)	p-value
Method of Tumour Identification					
Asymptomatic Screening	28 (58)	40 (55)	57 (54)	234 (51)	0.645
Symptomatic Work-up	20 (42)	32 (44)	49 (46)	229 (49)	
Disease Stage (TMN)					
Stage 0 - 2	15 (31)	20 (28)	20 (19)	107 (23)	0.332
Stage 3 - 4	34 (69)	52 (72)	86 (81)	356 (77)	
% neighborhood pursuing post-secondary education					
> 40%	15 (31)	31 (44)	54 (51)	185 (40)	**0.027**
31-40%	13 (27)	22 (31)	27 (26)	166 (36)	
< 31%	21 (43)	18 (25)	24 (22)	111 (24)	
% neighborhood who are immigrants					
> 30%	15 (31)	29 (40)	21 (20)	127 (28)	**0.003**
21-30%	22 (45)	21 (30)	28 (27)	145 (31)	
< 21%	12 (24)	21 (30)	56 (53)	190 (41)	
Income Quintiles					
1 (lowest)	19 (39)	14 (20)	14 (13)	94 (21)	**<0.001**
2	10 (20)	14 (20)	24 (23)	88 (19)	
3	5 (10)	10 (14)	15 (14)	111 (24)	
4	9 (18)	17 (24)	17 (16)	91 (20)	
5 (highest)	6 (12)	16 (22)	35 (33)	75 (16)	
Age at diagnosis					
≤ 50 years	9 (18)	17 (23)	19 (18)	97 (21)	0.844
51 – 70 years	25 (51)	35 (49)	50 (47)	237 (51)	
> 70 years	15 (31)	20 (28)	37 (35)	129 (28)	
Obese (BMI > 30)					

Yes	14 (30)	35 (51)	39 (38)	158 (36)	0.072
No	33 (70)	34 (49)	63 (62)	285 (64)	
Employment					
Employed	14 (30)	30 (42)	35 (33)	187 (41)	**0.002**
Not employed	21 (44)	16 (23)	24 (23)	79 (18)	
Retired	13 (27)	25 (35)	46 (44)	186 (41)	
Marital Status					
Married	27 (55)	47 (65)	70 (67)	287 (62)	0.535
Not married	22 (45)	25 (35)	35 (33)	175 (38)	
First Degree Relative with BC					
Yes	9 (24)	17 (26)	26 (26)	102 (23)	0.913
No	29 (76)	48 (74)	76 (74)	342 (77)	
Smoking History					
Smoker or previous smoker	18 (37)	25 (36)	49 (46)	184 (40)	0.511
Never smoked	31 (63)	44 (64)	57 (54)	277 (60)	
Comorbidities					
None	12 (25)	18 (25)	26 (24)	116 (25)	0.999
1 or more	37 (75)	54 (75)	80 (76)	347 (75)	
Location Primary Imaging					
OBSP	12 (24)	25 (35)	37 (35)	176 (39)	**0.043**
Hospital	19 (39)	29 (41)	52 (49)	198 (43)	
Non-hospital Clinic	18 (37)	17 (24)	17 (16)	82 (18)	
Imaging in past 2 years					
Yes	14 (33)	28 (44)	45 (48)	217 (54)	0.050
No	28 (67)	35 (56)	49 (52)	187 (46)	
Previous Breast Cancer					
Yes	2 (4)	5 (7)	16 (15)	62 (13)	0.100
No	47 (96)	67 (85)	90 (85)	401 (84)	

BC – breast cancer; FFS – Fee-for-Service; EFFS – Enhanced Fee-for-Service; FHO – Family Health Organization; FHO-FHT – Family Health Organization with Allied Family Health Team; BMI – body mass index; OBSP – Ontario Breast Screening Program;

Table 4. Univariate analysis of socioeconomic factors vs. methods of tumour identification and stage at diagnosis.

Variables	Asymptomatic Screening (n=337)	Symptomatic Work-up (n=383)	p-value	Stage 0-2 (n=545)	Stage 3-4 (n=176)	p-value
	n (%)	n (%)		n (%)	n (%)	
Age at Diagnosis						
< 51 years	37 (11)	112 (29)	**<0.001**	102 (19)	47 (27)	**0.044**
51-70 years	220 (65)	143 (37)		287 (53)	77 (44)	
> 70 years	80 (24)	128 (33)		156 (29)	52 (30)	
Obese (BMI > 30)						
Yes	130 (40)	124 (34)	0.074	188 (36)	67 (39)	0.531
No	192 (60)	243 (66)		330 (64)	105 (61)	
Employment						
Employed	125 (38)	152 (40)	**0.001**	203 (38)	74 (43)	**0.006**
Not employed	53 (16)	98 (26)		103 (19)	48 (28)	
Retired	150 (46)	128 (34)		227 (43)	52 (30)	
Marital Status						
Married	218 (65)	228 (60)	0.152	351 (66)	96 (55)	0.056
Not married	118 (35)	154 (40)		99 (18)	42 (24)	
First Degree Relative with BC						
Yes	91 (28)	68 (19)	**0.005**	134 (26)	25 (15)	**0.003**
No	231 (72)	288 (81)		378 (74)	141 (85)	
Smoking History						
Smoker/previous smoker	134 (40)	155 (41)	0.807	215 (40)	74 (43)	0.468
Never smoked	201 (60)	224 (59)		327 (60)	99 (57)	
Comorbidities						
None	77 (23)	106 (28)	0.145	140 (26)	43 (24)	0.739
≥ 1	260 (77)	277 (72)		405 (74)	133 (76)	

Income Quintiles						
1 (lowest)	66 (20)	80 (21)		111 (21)	36 (21)	
2	63 (19)	78 (21)		99 (18)	42 (24)	
3	75 (22)	73 (19)	0.464	112 (21)	36 (21)	0.496
4	71 (21)	69 (18)		111 (21)	29 (17)	
5 (highest)	58 (17)	81 (21)		107 (20)	32 (18)	
% neighborhood pursuing post-secondary education						
> 40%	145 (43)	159 (42)	0.597	222 (41)	82 (47)	0.332
31-40%	104 (31)	132 (35)		186 (34)	51 (29)	
< 31%	86 (26)	91 (24)		135 (25)	42 (24)	
% neighborhood who are immigrants						
> 30%	95 (27)	104 (27)	0.466	152 (28)	47 (27)	0.653
21-30%	110 (33)	113 (30)		173 (32)	51 (29)	
< 21%	130 (39)	165 (43)		218 (40)	77 (44)	
Location Primary Imaging						
OBSP	--	--		222 (41)	36 (21)	**<0.001**
Hospital	--	--		229 (42)	85 (50)	
Non-hospital clinic	--	--		92 (17)	48 (28)	
Imaging in last 2 years						
Yes	204 (67)	113 (35)	**<0.001**	263 (55)	54 (37)	**<0.001**
No	102 (33)	210 (65)		220 (45)	93 (63)	
Previous BC						
Yes	49 (15)	38 (10)	0.058	71 (13)	16 (9)	0.163
No	288 (85)	345 (90)		474 (87)	160 (91)	
PCP Model						
FFS	20 (6)	28 (8)		34 (6)	15 (9)	
EFFS	32 (10)	10 (11)	0.645	52 (10)	20 (12)	0.332
FHO	49 (15)	57 (16)		86 (16)	20 (12)	
FHO-FHT	229 (69)	234 (65)		356 (67)	107 (66)	

BC – breast cancer; BMI – body mass index; ; FFS – Fee-for-Service; EFFS – Enhanced Fee for Service; FHO – Family Health Organization; FHO-FHT –Family Health Organization with Allied Family Health Team; PCP - primary care physician; OBSP – Ontario Breast Screening Program

Table 5. Multivariable analyses exploring the predictors of tumour identification by asymptomatic screening and early disease stage at diagnosis.

Variable	Odds ratio (95% CI)	p-value
Predictors of asymptomatic screening vs. symptomatic work-up (n=532)		
Age at Diagnosis – < 51 years	Ref	
51–70 years of age	4.30 (2.60, 7.20)	**<0.001**
>70 years of age	2.12 (1.22, 3.68)	**0.007**
Obese (BMI > 30)	1.53 (1.03, 2.267)	**0.035**
Not employed	0.52 (0.32, 0.85)	**0.009**
Imaging in past 2 years	3.00 (2.05, 4.42)	**<0.001**
Hosmer-Lemeshow p-value = 0.369		
Predictors of early stage disease at diagnosis (Stage 0-2) vs. late stage (stage 3-4) (n=531)		
First degree relative with BC	2.25 (1.32, 3.85)	**0.003**
Location Primary Imaging		
Non-hospital clinic	Ref	
Hospital	1.14 (0.69, 1.90)	0.603
OBSP	2.96 (1.67, 5.25)	**<0.001**
Hosmer-Lemeshow p-value = 0.375		

OBSP – Ontario Breast Screening Program; BC – breast cancer; BMI – body mass index; CI – confidence interval

screening for women aged 51-70 years, for cases with imaging in the last two years and those with a 1st degree relative with breast cancer ($p< 0.05$). Women aged 51 – 70 years and women who were retired were more likely to have their breast cancer diagnosed at an earlier stage. Women who had their imaging performed at OBSP and imaging performed within the last two years as well as women having a first degree relative with breast cancer were also more often diagnosed at an earlier stage.

Table 5 presents multivariable analyses of SES, patient factors, and method of tumour identification as well as stage at diagnosis. Independent predictors of cancer detection with asymptomatic screening included: older age (OR 4.30 for patients who were diagnosed with breast cancer at age 51-70 compared to women < 51 years, OR 2.12 for patients above age 70 compared to women < 51 years); being obese (OR 1.53), and patients who had imaging within the past two years (OR 3.00). Unemployed patients were less likely to have their breast cancer diagnosed through asymptomatic screening (OR 0.52) compared to women who were employed or retired. Predictors for early stage disease at diagnosis included patients with a first-degree relative with breast cancer (OR 2.25) and patients who had their primary imaging at OBSP. Those diagnosed through OBSP were more likely to be diagnosed early (OR 2.96) compared to those who had their imaging at a non-hospital clinic.

Discussion

Breast cancer management and outcomes can be affected by a wide-range of factors and SES may be an important contributor.[4,5] One of the most potent prognostic factors for breast cancer outcome is early diagnosis[2,3]. In our study we specifically examined early detection of breast cancer, defined as diagnosis by asymptomatic screening and diagnosis at an early stage. Our hypothesis was that SES level may be related to breast cancer screening and diagnosis, in light of the association between breast cancer mortality by neighbourhood SES reported by Johnston et al. in the Hamilton region.[40] However, we found that area-level income, education, and immigration status did not affect the rate of early detection of breast cancer. We also found no association between area-level income and stage at diagnosis. Booth et al.[12] and Brewster et al.[44] , also found a lack of strong association between stage at diagnosis and income in cohorts from Ontario, Canada and in the UK. In comparison, several US studies[4,20] found that patients with lower socioeconomic status were more likely to be diagnosed with more advanced disease. Gorey[45] found that the rate of early breast cancer diagnosis in Ontario was significantly better than the rate for US women uninsured or Medicaid/Medicare insured in California. Both Canada and the UK have universal health care systems that may provide better access to breast cancer screening.

Such results may be partially attributable to ongoing efforts in promoting breast cancer screening through media and PCP offices.[46] In Hamilton, a “Screen for life” bus initiative offered more than 600 people breast cancer breast cancer screening each year, targeting areas with low SES, difficult access to screening centres, and certain cultural groups identified as being less

familiar with cancer screening.[47,48] Such programs have also been utilized in remote areas of Northern Ontario where healthcare accessibility is an issue.

Predictors of breast cancer detection from screening included patients in the recommended screening age range (51-70 years) and with a body mass index greater than 30 where a breast lump was more likely non-palpable. Patients with a first degree relative with breast cancer, a personal history of breast cancer, and regular screening within the past two years were more likely to have their breast cancer diagnosed through screening and at an earlier stage. Patients with a previous diagnosis of breast cancer or strong family history were likely more educated and sensitive to their screening, leading to earlier diagnoses. Other studies have found that attendees for breast screening were more likely to have breast cancer in their family or among friends.[49,50]

Lack of accessibility to primary care has been associated with lower rates of cancer screening.[28,51] In our study cohort only 11 out of 721 patients (1.5%) did not have a PCP, and these cases had a higher percentage of breast tumours detected by symptomatic presentation and at an advanced stage. This is consistent with the literature and highlights the benefit of primary care and regular screening.[34] Although efforts have been made to connect patients with PCPs through the Health Care Connect Program in Ontario (telephone/online registry to match prospective patients with available PCPs)[52], some patients still do not have a regular PCP. Interestingly, only 1.5% of patients in our study cohort did not have PCP, which suggests that a shortage of PCPs or access to PCPs may not be as great a problem in Hamilton (for women similar to those in our cohort) as in other areas of Ontario. Almost 80% of patients in our Hamilton cohort were enrolled in a capitation-based model (FHO or FHO-FHT), which is higher than results found in other Ontario metropolitan/urban areas.[24,33,34]

To the authors' knowledge, this study is the first study to examine the relationship between PCP model and method of identification and stage at diagnosis of breast cancer. We postulated that patients enrolled in a PCP model with incentives as a part of remuneration may have more breast cancer detected through screening. However, no such association was found in our cohort, although FHO/FHO-FHT patients more often had their breast cancer diagnosed through OBSP, rather than at a non-hospital clinic, compared to FFS and were more likely to have had imaging in the past two years (although this did not reach statistical significance). We found differences in patient characteristics treated by different PCP models similar to those found by Glazier et al.[36] FFS-based models had more patients living in neighbourhoods with a higher percentage of immigrants and more unemployed patients compared to FHO/FHO-FHT models. Other studies examining PCP characteristics and cancer screening in metropolitan and urban areas in Canada found that rates of breast cancer and cervical cancer screening were highest in enrolled PCP models with incentives for preventative care and lowest in those in straight FFS or receiving no PCP care.[24,28] Interestingly, a longitudinal study by Kiran et al.[53] found that PCP models receiving incentives for cancer screening showed little or no increase in cancer screening rates (3% increase for breast cancer) in Ontario in the three years after widespread implementation of the program, suggesting that pay-for-performance incentives had little impact.

Our analysis found that unemployed patients were less likely to have their breast cancer diagnosed by asymptomatic screening. Lagerlund et al.[48,54] found that women who were not regularly employed were twice as likely to be non-attenders for mammography screening in a universal health care system with an outreach screening program and a UK study by Coyle et al.[55] found a similar result. Li et al.[56] found that being employed predicted compliance with chemotherapy, radiation, and hormonal therapy in a cohort of breast cancer patients. Langerlund suggests that employment status may serve as a proxy for degree of social integration.[54]

A strength of our study is that the clinical and demographic data were obtained directly from patient charts, which allowed us to retrieve extensive and accurate data.[57-58] Despite this strength, chart reviews are limited to the information contained within a patient's chart. We used area-level data from the Canadian Census for income, immigration status, and education as a proxy for individual level data as these variables were not available in the patient chart. Ecological fallacy (e.g., the tendency that those living in lower SES neighbourhood may not be of low SES) may occur when using area-level data to estimate individual-level data, although the use of ecological income is generally accepted as valid and is commonly used in health services research.[59-61] The sample size for FFS and EFFS groups was smaller than expected and this may have limited our ability to detect a difference between PCP models. This study was also restricted to the Hamilton region, which may limit the generalizability of our results to other jurisdictions with different types and distributions of PCP models and without universal health care. Inclusion of a wider, rural/urban region would potentially be more representative, provide a larger, more varied sample, and enable a more robust and detailed analysis.

Conclusions

Area-level SES variables did not affect early detection of breast cancer by diagnosis through screening or diagnosis at an early stage in our study cohort from an urban Canadian centre. Likewise, PCP models did not have a significant impact on breast cancer detection or stage at diagnosis, but these results may be compromised by our limited sample size. Our results suggest that early detection of breast cancer is not dependent on SES variables in our urban setting within a universal health care system with readily available primary care for the vast majority of women. There are numerous models of primary care delivery and many factors that can affect cancer diagnosis and management. This study demonstrates that research into these factors can yield important information and knowledge that can impact access to care. Possible differences in access to care, or processes of care based on the type of PCP deserve further study.

Conflicts of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

Funding was provided by a grant from the McMaster Surgical Associates. The funding source played no role in the design, conduct or reporting of this study.

Acknowledgments

We would like to thank Jane Walker, Physician Recruitment Specialist from Hamilton Physicians, for assistance with identifying primary care models for our study cohort.

References

1. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2018. Toronto, ON: Canadian Cancer Society; 2018. Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN [accessed online April 8, 2019]. June 2018. ISSN 0835-2976/.
2. Taghian A, El-Ghamry MN, Merajver SD. Overview of the treatment of newly diagnosed, non-metastatic breast cancer. UpToDate 2015, Retrieved July 11, 2018 from the World Wide Web: https://www.uptodate.com/contents/overview-of-the-treatment-of-newly-diagnosed-non-metastatic-breast-cancer.
3. Cancer Care Ontario. Toronto: Breast Cancer Screening (update 2015), Retrieved July 11, 2018 from the World Wide Web: https://www.cancercareontario.ca/en/types-of-cancer/breast-cancer/screening?redirect=true.
4. Woods LM, Rachet B, Coleman PM. Origins of socio-economic inequalities in cancer survival: A review. Ann Oncol 2006; 17: 5-19.
5. Sprague BL, Trentham-Dietz A, Gangnon RE, et al. Socioeconomic status and survival after an invasive breast cancer diagnosis. Cancer 2011; 117: 1542-51.
6. Vona-Davis L, Rose DP. The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review. J Womens Health 2009; 18: 883-93.
7. Klassen AC, Smith KC, The enduring and evolving relationships between social class and breast cancer burden: a review of the literature. Cancer Epidem 2011; 35: 217-34.
8. Potosky AI, Merrill RM, Riley GF, et al. Breast cancer survival and treatment in health maintenance organization and fee-for-service settings. J Natl Cancer Inst 1997; 89: 1683-91.
9. Aarts, MJ, Hamelinck VC, Bastiaannet E, et al. Small but significant socioeconomic inequalities in axillary staging and treatment of breast cancer in the Netherlands. Br J Cancer 2012; 107: 12-17.
10. Dasgupta P, Baade PD, Aitkens JF, et al. Multilevel determinants of breast cancer survival: association with geographic remoteness and area-level socioeconomic disadvantage. Breast Cancer Res Treat 2012; 132: 701-10.
11. Mackillop WJ, Zhang-Salomons J, Groome PA, et al. Socioeconomic status and cancer survival in Ontario. J Clin Oncol 1997; 15: 1680-9.

12. Zhang-Salomons J, Qian H, Holowaty E, et al. Association between socioeconomic status and cancer survival: choice of SES indicator may affect results. Ann Epidem 2006; 16: 521-8.
13. Booth CM, Li G, Zhang-Salomons J, et al. The impact of socioeconomic status on stage of cancer at diagnosis and survival: A population-based study in Ontario, Canada. Cancer 2010; 116: 4160-7.
14. Kumachev A, Trudeau ME, Chan KKW. Associations among socioeconomic status, patterns of care, and outcomes in breast cancer patients in a universal health care system: Ontario's Experience. Cancer 2016; 122: 893-8.
15. Borugian MJ, Spinelli JJ, Abanto Z, et al. Breast cancer incidence and neighbourhood income. Statistics Canada, Catalogue no. 82-003-XPE, Health Reports 2011; 22: 1-7.
16. Katz SJ, Zemencuk JK, Hofer TP. Breast cancer screening in the United States and Canada, 1994: socioeconomic gradients persist. Am J Public Health 2000; 90: 799-803.
17. Maddison AR, Asada Y, Urquhart R. Inequity in access to cancer care: a review of the literature. Cancer Causes Control 2011; 22: 359-66.
18. Coburn N, Fulton J, Pearlman DN, et al. Treatment variation by insurance status for breast cancer patients. Breast J 2008; 14: 128-34.
19. Paszat LF, Mackillop WJ, Zhang-Salomons J, et al. Radiotherapy for breast cancer in Ontario: Rate variation associated with region, age and income. Clin Invest Med 1998; 21: 125-34.
20. Gorey KM, Luginaah IN, Holowaty EJ, et al. Wait times for surgical and adjuvant radiation treatment of breast cancer in Canada and the United States: greater socioeconomic inequity in America. Clin Invest Med 2009; 32: E239-E249.
21. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. Cancer Causes Control 2009; 20: 417-35.
22. Sun Z, Xiong H, Kearney A, et al. Breast cancer screening among Asian immigrant women in Canada. Cancer Epidem 2010; 34: 73-8.
23. Lofters AK, Moineddin R, Hwang SW, et al. Low rates of cervical cancer screening among urban immigrants: A population-based study in Ontario, Canada. Med Care 2010; 48: 611-18.
24. Vahabi M, Lofters AK, Kumar M, et al. Breast cancer screening disparities among urban immigrants: a population-based study in Ontario, Canada. BMC Public Health 2015; 15: 679.
25. Barkoff CM, Saskin R, Rabeneck L, et al. Disparities in receipt of screening tests for cancer, diabetes and high cholesterol in Ontario, Canada: A population-based study using area-based methods. Can J Public Health 2013; 104: e284-e290.
26. Gorey KM. Breast cancer survival in Canada and the USA: meta-analytic evidence of a Canadian advantage in low-income areas. Int J Epidemol 2009; 38:1543-51.

27. Gorey KM, Kliewer E, Holowaty EJ, et al. An international comparison of breast cancer survival: Winnipeg, Manitoba and Des Moines, Iowa, metropolitan areas. Ann Epidem 2003; 13: 32-41.
28. Lofters AK, Ng R, Lobb R. Primary care physician characteristics associated with breast cancer screening: a retrospective cohort study in Ontario, Canada. Cancer Med 2015: 4: 212-23.
29. Sutradhar R, Gu S, Glazier RH et al. The association between visiting a primary care provider and uptake of periodic mammograms as women get older. J Med Screen 2016: 23: 83-8.
30. Esteva M, Ripoll J, Leiva A, et al. Determinants of non-attendance to mammography program in a region with high voluntary health insurance coverage. BMC Public Health 2008; 8: 387.
31. Gorey KM, Luginaah IN, Holowaty EJ, et al. Associations of physician supplies with breast cancer stage at diagnosis and survival in Ontario, 1988 to 2006. Cancer 2009; 115: 3563-70.
32. Physician Shortage in the US threatens physician supply in Ontario. News Release, May 2012. Ontario MedicaAssociation. https://www.oma.org/Mediaroom/PressReleases/Pages/ Physician Shortage.Niagara.aspx. Accessed Dec 6. 2013.
33. Ontario Medical Association (OMA). "Primary Care Compensation Models," HNHB Board Presentation, April 2011. Retrieved July 11, 2018 from the World Wide Web: file:///C:/Users/scornacc/Downloads/Primary%20Care%20Compensation%20Models%20-%20LHIN%20Presentation%20-%20Wooder-FINAL%20revised.pdf.
34. Green ME, Gozdyra P, Frymire E, Glazier RH. Geographic Variation in the Supply and Distribution of Comprehensive Primary Care Physicians in Ontario, 2014/15. Toronto, ON: Institute for Clinical Evaluative Sciences; 2017. ISBN 978-1-926850-75-7 (Online). [Accessed online April 8, 2019].
35. Ministry of Health and Long Term Care, Ontario. Family Medicine Compensation and Practice Models in Ontatio, June 26, http://www.healthforceontario.ca/ UserFiles/file/ PracticeOntario/FM%20Compensation%20Practice%20Models%20EN.pdf [Accessed online April 8, 2019]
36. Glazier RH, Hutchison BG, Kopp A. Comparison of family health teams to other primary care models 2004/05 to 2011/12. Toronto: Institute for Clinical Evaluative Sciences (ICES); 2015.
37. Glazier RH, Klein-Geltink J, Kopp A, et al. Capitation and enhanced fee-for-service models for primary care reform: a population-based evaluation. CMAJ 2009; 180: E72-E81.
38. Glazier RH, Zagorski BM, Rayner J. Comparison of primary care models in Ontario by demographics, case mix and emergency department use, 2008/09 to 2009/10. Toronto: Institute for Clinical Evaluative Sciences (ICES); 2012.
39. DeLuca PF, Buist S, Johnston N. The Code Red Project: Engaging communities in health system change in Hamilton, Canada. Soc Indic Res 2012; 108: 317-27.

40. Johnston N, Buist S, DeLuca PF. Code Red, Day 2: Spotlight on breast cancer. Hamilton Spectator, 2013. Retrieved July 11, 2018 from the World Wide Web: Available at: http://thespec-codered.com.
41. Paddon N. Hamilton has more doctors in family health teams despite physician shortage. Hamilton Spectator, July 12, 2017. https://www.thespec.com/news-story/7418388-hamilton-has-more-doctors-in-family-health-teams-despite-physician-shortage/ [Accessed online on April 8, 2019]
42. Town R, Kane R, Johnson P, Butler M. Economic incentives and physicians' delivery of preventive care: a systematic review. Am J Prev Med 2005; 28(2): 234-240.
43. Schultz SE, Simunovic M, Urbach DR. Cancer Surgery in Ontario: ICES Atlas, Technical Appendix. Toronto: Institute for Clinical Evaluative Sciences (ICES), 2008, pp.TA4-TA5.
44. Brewster DH, Thomson CS, Hole DJ, et al. Relation between socioeconomic status and tumor stage in patients with breast, colorectal, ovarian, and lung cancer: results from four national, population based studies. BMJ 2001; 322: 830-1.
45. Gorey KM, Richter NL, Luginaah IN, et al. Breast cancer among women living in poverty: Better care in Canada than in the United States. Soc Work Res 2015; 39:107-118.
46. Baron RC, Melillo S, Rimer BK, et al. Intervention to increase recommendation and delivery of screening for breast, cervical, and colorectal cancers by healthcare providers a systematic review of provider reminders. Am J Prev Med 2010; 38:110–117.
47. Chapman T. Cancer screening bus rolls onto Hamilton streets. CBC News, 2013. Retrieved July 11, 2018 from the World Wide Web: https://www.cbc.ca/news/canada/hamilton/headlines/cancer-screening-bus-rolls-onto-hamilton-streets-1.1362640.
48. Craggs S. "Hamilton cancer-screening bus 'saved my life'," CBC News, 2014. Retrieved July 11, 2018 from the World Wide Web: https://www.cbc.ca/news/canada/hamilton/headlines/hamilton-cancer-screening-bus-saved-my-life-1.2724044.
49. Lagerlund M, Sparen P, Thurfjell E, et al. Predictors of non-attendance in a population-based mammography screening programme; socio-demographic factors and aspects of health behavior. Eur J Cancer Prev 2000; 9: 25-33.
50. Hodgson SV, Mohammed SN. "Consider family history also". Comment on Sutton GC, Balmer S. Screening for breast cancer: Screen women over 65. BMJ 1994; 309: 664.
51. Poole B, Black C, Gelmon K, Kan L. Is Canadian women's breast cancer screening behaviour associated with having a family doctor? Canadian Family Physician. 2010; 56(4): e150–157.
52. Health Care Connect, "Find a family doctor or nurse practitioner," Ministry of Long-Term Health, 2016. Retrieved July 11, 2018 from the World Wide Web: https://www.ontario.ca/page/find-family-doctor-or-nurse-practitioner#section-0.
53. Kiran T, Wilton AS, Moineddin R, et al. Effect of payment incentives on cancer screening in Ontario primary care. Ann Fam Med 2014; 12: 317-23.

54. Lagerlund M, Maxwell ME, Bastani R, et al. Sociodemographic predictors of non-attendance at invitational mammography screening – a population-based register study (Sweden). Cancer Causes Control 2002; 13: 73-82.
55. Coyle C, Kinnear H, Rosato M, et al. Do women who intermittently attend breast screening differ from those who attend every invitation and those who never attend? J Med Screen 2014; 21: 98-103.
56. Li J, Cornacchi SD, Farrokhyar F, et al. The relationship between socioeconomic variables and surgical, systemic and radiation treatment in a cohort of breast cancer patients in an urban Canadian Centre. Can J Surg 2019; 62(2):83-92.
57. Kim HM, Goodman M, Kim BI, et al. Frequency and determinants of missing data in clinical and prognostic variables recently added to SEER. J Registry Manag 2011; 38:120-31.
58. Du XL, Key CR, Dickie L, et al. Information on chemotherapy and hormone therapy from tumor registry had moderate agreement with chart reviews. J Clin Epidemiol 2006; 59:53-60.
59. Subramanian SV, Chen JT, Rehkopf DH, et al. Comparing individual- and area-based socioeconomic measure for the surveillance of health disparities: a multilevel analysis of Massachusetts births, 1989-1991. Am J Epidem 2006; 164: 823-34.
60. Krieger N. Overcoming the absence of socioeconomic data in medical records: Validation and application of a census-based methodology. Am J Public Health 1992; 82: 703-10.
61. Denny K, Davidson MJ. Area-based socio-economic measures as a tool for health disparities research, policy and planning. Can J Public Health 2012; 103 (suppl.2): S4-6.

Case Report Original Research Article

Massive obscure GI bleeding from idiopathic jejunal varices identified using single balloon enteroscopy

Natasha Harris[a], Alaa Rostom[b], and Husein Moloo[c]

[a]University of Ottawa, Ottawa, Canada

[b]Faculty of Medicine, Division of Gastroenterology, The Ottawa Hospital, Ottawa, Canada

[c]Department of General Surgery, The Ottawa Hospital, Ottawa, Canada

Abstract

Background: Obscure gastrointestinal bleeding from idiopathic small bowel varices is both a diagnostic and management challenge for physicians. There are very few cases reported in the literature and there is no consensus on management recommendations.

Aims: To present the case of a 34-year-old male patient with bleeding from idiopathic jejunal varices and to review similar cases in the literature.

Methods: A case of idiopathic jejunal varices is reported. A literature review was conducted and a total of 25 articles describing idiopathic small bowel varices were identified.

Results: Case Report: A 34-year-old gentleman was referred for worsening obscure gastrointestinal bleeding and anemia. Anterograde single balloon enteroscopy revealed several petechial like lesions that were not classic for angiodysplasia. These lesions were initially treated with argon plasma coagulation and clipped, which did not resolve the patient's persistent anemia**.** No venous abnormalities were identified on computed tomography of the abdomen and pelvis with contrast. The patient underwent an endoscopically assisted exploratory laparoscopy that was converted to a laparotomy upon finding of grossly abnormal distal jejunum. Dilated and tortuous varicosities were identified involving approximately 150 cm of small bowel. It was decided to resect the 40 cm segment of jejunum in which varices were visible endoscopically. There was no evidence of thrombosis in the resected specimen. The patient suffered a pulmonary embolism post-operatively, believed to be provoked by the surgery. The patient has had no re-bleeding 12 months post-resection.

Literature Review: Both familial and non-familial accounts of small bowel varices in the absence of a primary cause have been reported in the literature. When supportive therapy is insufficient, the most common treatment modality chosen is surgical resection. Select cases have also demonstrated that sclerotherapy and varix dissection can be used for to treat these lesions.

Conclusions: Idiopathic small bowel varices pose both diagnostic and therapeutic challenges for physicians. In the literature, several treatment modalities have been shown to be successful; these include surgical resection, varix dissection and sclerotherapy. There is no consensus on the preferred treatment strategy. This report demonstrates endoscopically assisted surgical resection as a viable management strategy for bleeding of idiopathic small bowel varices, an uncommon cause of occult GI bleeding.

Keywords: Single balloon enteroscopy; jejunal varices; case report; GI bleeding

Corresponding author: nharr024@uottawa.ca

Introduction

Bleeding from the small intestine is a relatively uncommon occurrence, accounting for only 5% of all gastrointestinal bleeds.[1] One of the causes of small bowel bleeds are ectopic varices, which are most frequently seen as a result of advanced liver cirrhosis and portal hypertension. Other important risk factors include pancreatitis and thrombosis. Rarely, instances of bleeding from idiopathic small bowel varices have been reported in the absence of any underlying cause. The lack of recognition of these lesions poses a diagnostic dilemma and there are few cases reported in the literature. The rarity of these lesions means that there is little information about their diagnosis and management. The high mortality and morbidity associated with gastrointestinal bleeding underlines the importance of prompt diagnosis and management, even when the cause of bleeding may be obscure. Although mortality rates of upper gastrointestinal bleeds vary between studies, one group demonstrated that the mortality of acute variceal bleeds is as high as 15%.[2] This report examines the diagnosis and treatment of idiopathic small bowel varices in a patient without any significant risk factors.

Purpose

This article reports the case of a 34-year-old male patient with bleeding from idiopathic jejunal varices. A literature search was conducted examining other instances of idiopathic varices in the small bowel.

Methods

A literature review was conducted in Pub Med with the following search terms

Varicose vein* OR varix	AND	Small bowel OR Small intestine OR duodenum OR ileum OR jejunum	AND	Gastrointestinal OR GI OR intestinal	AND	Bleed* OR hemorrhage OR melena OR hematemesis OR iron deficiency anemia
Filters : Case report; Meta-analysis; Review; Systematic Reviews				Languages : French; English		

This yielded a total of 355 results. Following initial screening of these results, 97 were marked as potentially relevant. Due to inconsistent search terms, articles included in the references of related articles were also reviewed. This allowed for an increase in the number of related articles

that were identified. A total of 25 articles describing idiopathic varices of the small bowel were found. Inclusion criteria was cases of small bowel varices with no underlying cause. Articles which did not rule out possible underlying causes of small bowel varices were excluded.

Case report

A 34-year-old gentleman was referred for worsening obscure gastrointestinal bleeding requiring more than 20 packed red blood cell (pRBC) transfusions over one month. The patient had a history of intermittent melena and anemia over the previous year. He was known for mild asthma and mild developmental delay, but no other significant medical history and specifically no history of liver disease, pancreatitis, or past thrombosis. He presented to emergency with a gastrointestinal bleed, with associated tachycardia and hypotension. Upper and lower endoscopies were non-diagnostic.

On further investigation by capsule endoscopy, he was thought to have potential angiodysplasia of the proximal jejunum. Esophagogastroduodenoscopy (EGD) was unremarkable. Anterograde single balloon enteroscopy revealed several petechial-like lesions that were not classic for angiodysplasia. These lesions were treated with argon plasma coagulation and clipped**.** However, distal to these lesions in the mid to distal jejunum, large redundant veins were observed although it was not clear over what distance these veins extended. The veins showed no signs of recent bleeding. Small bowel varices were suspected but not treated pending further evaluation. The site was clipped proximal to the veins.

A follow-up computed tomography with contrast of the abdomen and pelvis was performed, and no specific varices or veins were identified. The patient was discharged home with a diagnosis of angiodysplasia bleeding with possible non-bleeding varices.

The patient was readmitted following a 3-week follow-up blood test which revealed significant iron deficiency anemia (hemoglobin 75g/L). Two days following the initial follow-up blood test, his anemia at admission had worsened (hemoglobin 69g/L) and he received 2 units of pRBCs. The patient was transferred the following day to a tertiary care center pending intervention and his repeat hemoglobin was 84 g/L. It was assumed that the bleed was likely from the small bowel varices. Patient workup confirmed no evidence of liver disease, portal hypertension, or thrombosis. The single balloon enteroscopy was repeated. There was no evidence of bleeding from the cauterized petechiae or from the visualized varices. (Figure 1)

Figure 1. Endoscopy images of the jejunal varices.

Sclerotherapy or histo-acryl glue injection were considered as possible treatment modalities, but it was felt that in the absence of portal hypertension, there was risk of mesenteric and/or portal vein thrombosis. There was concern that there might be further congenital vascular anomalies or hematologic abnormalities that could increase this patient's risk of thrombosis. Furthermore, because the lesion was only visible at the limit of the scope insertion, there was poor control over the needle at the insertion site. As there is no consensus on the preferred treatment modality of jejunal varices in the literature, it was thus decided that the preferred management of the bleeding would be by surgical resection. The site was tattooed.

The patient underwent an endoscopically assisted exploratory laparoscopy that was converted to a laparotomy upon finding of grossly abnormal distal jejunum. The varicose veins extended to just proximal to the ileocecal valve, which was 100 cm proximal to the ligament of Treitz. Interestingly, there were 150 cm of dilated varicosities visible on the exterior of the small bowel, but only 40 cm of the lesion penetrated the submucosa and was visible endoscopically. The colon, mesentery, and mesenteric vasculature appeared normal. The decision was made to resect the 40 cm segment of jejunum for which varices were visible endoscopically. (Figure 2)

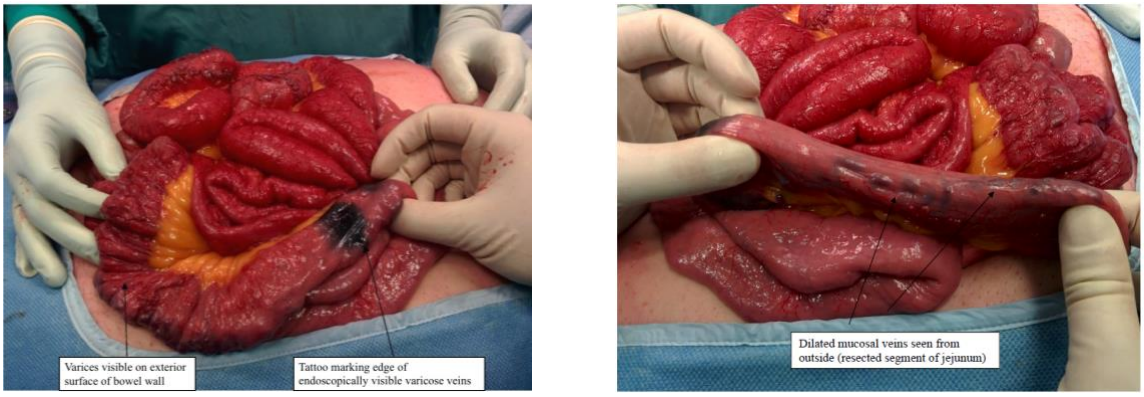


Figure 2. a) left: Surgical images demonstrating the visibly engorged veins and the endoscopic tattoo b) Right: Dilated veins visible on exterior of bowel wall.

The patient suffered a pulmonary embolism post-operatively 3 days following the resection. The patient presented with hypoxemia and mild chest tightness. Computed tomography pulmonary angiography (CT-PA) confirmed the presence of 2-segmental pulmonary emboli. Following workup and thrombosis consultation, it was determined that this event appeared to be provoked by the surgery. The patient was anticoagulated with Warfarin post-discharge and convalesced without further complications. He was prescribed ferrous fumarate 300mg daily. The patient has had no re-bleeding 8 months post-resection. The patient's hemoglobin increased steadily post-resection and was 107 g/L at his 8-month follow-up appointment. His ferritin remained low at 6ug/L, however, he was no longer experiencing melena stools and had no other evidence of bleeding.

Discussion

The small bowel is the least common site for gastrointestinal bleeding, however, it is the most common area for bleeds of an obscure nature.[3] The most common site of varices in the small intestine is the duodenum, but lesions may also appear in the jejunum and ileum.[4,5] Since gastrointestinal bleeding is often initially investigated using EGD and colonoscopy, lesions that lie outside the limits of these procedures are missed. In addition, not all small-bowel varices penetrate the submucosa so physicians must be aware that these lesions may not be identified endoscopically.[6] Capsule endoscopy and CT angiography are second line imaging modalities used to identify the source of the bleeding. Specialized endoscopic procedures, such as balloon enteroscopy, can also be used to investigate lesions outside the limits of standard endoscopes. Targeted red blood cell scans have also been used in instances of active bleeding.[7] The success of these new investigative techniques has slowly replaced small bowel radiography.[5]

There is no standardized definition of small bowel varices that occur in the absence of an identifiable underlying cause. The presence of unexplained engorged veins in the small bowel has been described as idiopathic, familial, congenital varices as well as intestinal phlebectasia without an underlying cause. As some authors consider these terms synonymous, we have included all of them in this article. Interventions for ectopic varices can be divided into pharmacological, endoscopic, radiological and surgical options and there is no standard treatment.[8]

A review of the literature identified 25 reports of idiopathic varices in the small intestine. (Table 1) There are reports of both isolated cases and lesions demonstrating evidence of genetic inheritance. (Table 1)

Table 1. Reports of Idiopathic Small-bowel Varices.

Case Report	Age at first bleed; Sex	Affected Site	Familial evidence	Treatment	Complications
Atin *et al.*, 1993[9]	14 M	Small and large bowel, rectum, oesophagus	Yes	Surgical resection	None

	17 F	Colon, rectosigmoid	Yes	None	N/A
Boland *et al.,* 2014[7]	16 M	Large bowel, fundus, proximal stomach	Yes	Supportive, transfusions prn, IV rabeprazole and octreotide	Continued mild bleeding
	13 M	Colon, duodenum, jejunum	Yes	Supportive, transfusions prn, IV rabeprazole and octreotide	None
Dray, X *et al.,* 2009[10]	37 F	Colon, ileum	No	Supportive, monthly octreotide acetate LAR injections	None
El-Dosoky *et al.,* 1994[11]	10 M	Small and large bowel, rectum, oesophagus	Yes	Past surgical resection	Continued bleeding
Eriguchi *et al.,* 1998[12]	49 F	60 cm beyond ligament of Treitz	No	Surgical resection	None
Feldman *et al.,* 1970[13]	87 F	Jejunum	Unknown	Surgical resection	None
Friedman *et al.,* 1990[14]	32 M	Jejunum	No	Surgical resection	None
Gentilli *et al.,* 2011[15]	20 F	large bowel, ileum	No	Surgical resection	None
Hanipah *et al.,* 2016[8]	61 F	Duodenum	Unknown	Endoscopic sclerotherapy histo-acryl blue	None
Kay & Wylie, 2006[16]	2 M	Colon, ileum	Suspected	None	N/A
Konishi *et al.,* 2010[17]	54 F	Ileum	Unknown	Surgical resection	None
Kumar *et al.* 1997[18]	75 F	Jejunum, esophagus	No	None	N/A
Lopes *et al.,* 2006[19]	64 M	rectosigmoid, ileum	No	Surgical resection	None
Mejia *et al.,* 1996[20]	26 F	Jejunum	No	Surgical resection	None
Morini *et al.,* 1993[21]	67 F	Colon, ileum, duodenum	Yes	Unknown	Unknown
	65 F	Colon, suspected small bowel	Yes	Unknown	Unknown
Ohmiya *et al.,* 2013[22]	58 M	Jejunum, oral cavity	Unknown	Endoscopic sclerotherapy polidocanol	None, repeat sclerotherapy required
Olano *et al.,* 2014[23]	80 F	Jejunum, ileum	Unknown	Conservative therapy, oral iron	None
	66 M	Jejunum. ileum	Unknown	Conservative therapy	Intermittent mild melena
Papnikolau *et al.,* 2012[24]	61 M	Ileum	Unknown	Endoscopic sclerotherapy histo-acryl blue	None
Patel *et al.,* 2008[25]	14 F	Jejunum	Unknown	Polypectomy of vessel containing polyp by wedge resection laparotomy	Unknown
Peoples *et al.,* 1981[26]	60 M	Jejunum, ileum	No	Conservative therapy, iron PO	Unknown
Richardson *et al.,* 1976[27]	56 M	Duodenum	Unknown	Varix dissection	None
Rudzki *et al.,* 2013[6]	53 F	Duodenum	Unknown	Surgical resection	Pleural effusion secondary to infection
Schilling *et al.,* 1996[28]	25 M	Colon, Ileum	No	None	N/A
Tang *et al.,* 2004[29]	62 F	Colon, duodenum	No	Conservative therapy, iron PO	N/A
Veuillemin *et al.,* 2004[30]	34 M	Colon, ileum	No	None	N/A

Surgical resection was the most common treatment modality chosen. Of the surgical cases, 8 had no post-operative complications. However, our patient did suffer a pulmonary embolism post-operatively and there was one reported case of a pleural effusion from a presumed chest infection.[6] It is important to note that there were no reports of massive re-bleeding in any of the patients who underwent surgical resection.

Certain less invasive treatment options have also been explored in the goals of reducing the risk of short bowel syndrome and other complications. Patients have been treated with octreotide acetate long-acting release, which successfully eliminated bleeding of idiopathic varices.[10] Richardson *et al.* reported a case in which variceal bleeding in the second portion of the duodenum was successfully treated by varix dissection from the entrance into the vena cava to its penetration of the duodenal wall.[27] The caval side of the vein was ligated. A full thickness of duodenal wall containing the entire varix was then excised. This patient did well post-operatively and there was no re-bleeding at 8-month follow-up. Endoscopic injection therapy with polidocanol was used to treat varices of the jejunum.[22] Polidocanol is a sclerosing agent that reduces varicosities by causing venous fibrosis. Although the procedure had to be repeated for relapsing phlebectasia, it did ultimately stop the gastrointestinal bleeding. Endoscopic histo-acryl blue injection sclerotherapy has also been used to treat idiopathic varices of the ileum and duodenum.[8,24] This was successful in both reported cases; no complications or occurrences of re-bleeding were reported.[8,24]

Based on the literature, there is no preferred management strategy of idiopathic varices of the small bowel. In patients with high surgical risk but low risk of thrombosis, the less invasive therapies such as sclerotherapy or histo-acryl glue injection may be the preferred management strategies. Furthermore, in patients who have large segments of affected bowel, surgery becomes a less favorable option due to the risk of short-bowel syndrome. However, in cases such as ours where there are suspected underlying venous abnormalities that may increase risk of thrombosis, limitations of endoscopic access to affected area, and relatively short segments of affected bowel, surgical resection becomes advantageous.

Conclusion

Idiopathic duodenal varices pose both diagnostic and therapeutic challenges for physicians. Presentations of gastrointestinal bleeds caused by these lesions can be acute or chronic. Several treatment modalities have been shown to be successful; these include surgical resection, varix dissection, and sclerotherapy. There is no consensus on the preferred treatment strategy. In the case of our patient, surgical resection of the affected portion of the bowel was effective in achieving hemostasis, however, the patient did suffer a pulmonary embolism post-operatively. This underlines the importance of assessing and managing the risk of thrombosis associated with surgical procedures. It is likely that with the advances of endoscopic techniques which enable

further intubation of the small bowel, such as double balloon endoscopy, these lesions may become easier to investigate.

Conflict of Interest

The authors have no conflict of interest to disclose.

References

1. Briley CA, Jackson DC, Johnsrude IS, Mills SR. Acute gastrointestinal hemorrhage of small-bowel origin. Radiology 1980 Aug; 136(2):317-319.
2. Tandon P, Bishay K, Fisher S, Yelle D, Carrigan I, Wooller K, et al. Comparison of clinical outcomes between variceal and non-variceal gastrointestinal bleeding in patients with cirrhosis. J Gastroenterolo Hepatol 2018 Oct; 33(10):1773-1779.
3. Otani K, Watanabe T, Shimada S, Hosomi S, Nagami Y, Tanaka F, et al. Clinical Utility of Capsule Endoscopy and Double-Balloon Enteroscopy in the Management of Obscure Gastrointestinal Bleeding. Digestion 2018 Feb 1; 97:52-58.
4. Mora-Soler A, Velasco-Guardado A, Acosta-Materan R, Umana-Mejia J, Jamanca-Poma Y, Calderon-Begazo R, et al. Endoscopic treatment of duodenal varices with cyanoacrylate. Rev Esp Enferm Dig 2013 Nov-Dec; 105(10): 629-623.
5. Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG Clinical Guidelines: Diagnosis and Management of Small Bowel Bleeding. Am J Gastroenterol 2015 Sep; 110(9): 1265-1287.
6. Rudzki S, Dryka T, Wilczynski P, Bernat P, Bicki J, Furmaga J, et al. Varices of the descending duodenum explored during emergency gastro-duodenal resection for upper gastrointestinal hemorrhage, Case Report. Pol Przegl Chir 2013 May; 85(5): 279-283.
7. Boland P, Leonard J, Saunders M, Bursey F. Familial idiopathic small-bowel and colonic varices in three sibblings. Endoscopy 2014 Oct; 46(10): 893-897.
8. Hanipah ZN, Jasmani AH, Limi L, Gee T. Idiopathic duodenal varix presenting as a massive upper gastrointestinal bleeding: A case report. Med J Malaysia 2016 Oct; 71(5): 294-295.
9. Atin V, Sabas JA, Cotana JR, Madriage M, Galan D. Familial varices of the colon and small bowel. Int J Colorect Dis 1993 Mar; 8(1): 4-8.
10. Dray X, Vahedi K, Odinot JM, Marteau P. Octreotide for recurrent intestinal variceal bleeding in patients without portal hypertension. Eur J Gastroenterol Hepatol 2009 Jul; 21(7): 836-839.
11. El-Dosoky MM, Reeders JW, Dol JA, Tytgat GN. Familial intestinal varices without portal hypertension: a case report. Eur J Radiol 1994 May; 18(2): 140-141.
12. Eriguchi N, Aoyagi S, Hara M, Miyazaki T, Tanaka M, Toyonaga A. Varices as a Cause of Massive Gastrointestinal Bleeding: A Case Report. Kurume Med J 1998 Jun 15; 45(2): 227-230.
13. Feldman PS, Toffler RB, Lowman RM. Isolated Jejunal Varix Presenting as a Small Bowel Mass, Radiology 1970 Jan; 94(1): 105-106.
14. Friedman E, Sydorak G. Massive Gastrointestinal Bleeding from "Varix" of the Jejunum. J Clin Gastroenterol 1990 Aug; 12(4): 482-483.

15. Gentilli S, Aronici M, Portigliotti L, Pretato T, Garavoglia M. Idiopathic ileo-colonic varices in a young patient. Updates Surg 2012 Sep; 64(3): 235-238.
16. Kay M, Wylie R. Image of the Month: Hereditary Colonic Varices. J Pediatr Gastroenterol Nutr 2006 Oct; 43(4): 409-410.
17. Konishi H, Kikuchi S, Miyashita A, Ichikawa D, Fujiwara H, Kubota T, et al. (2010). Minimally Invasive Surgery for Obscure Idiopathic Ileal Varices Diagnosed by Capsule Endoscopy and Double Balloon Endoscopy: Report of a Case. Surg Today 2010 Nov; 40(11): 1088-1092.
18. Kumar P, Salcedo J, Al-Kawas FH. Enteroscopic diagnosis of bleeding jejunal phlebectasia: a case report and review of literature. Gastrointestinal Endosc 1997 Aug; 46(2): 185-187.
19. Lopes LM, Ramada JM, Certo MG, Pereira PR, Soares JM, Ribeiro M, et al. Massive Lower Gastrointestinal Bleeding From Idiopathic Ileocolonic Varix: Report of a Case. Dis Colon Rectum 2006 Apr; 49(4): 524-526.
20. Mejia EM, Alvarez OA, Anderson EC, Encarnacion CE, Luna M, Tio FO, et al. Jejunal phlebectasia presenting with massive gastrointestinal hemorrhage. J Clin Gastroenterol 1996 Apr; 22(3): 215-217.
21. Morini S, Caruso F, De Angelis P. Familial Varices of the Small and Large Bowel. Endoscopy 1993 Feb; 25(2): 188-190.
22. Ohmiya N, Nakamura M, Funasaka K, Miyahara R, Ohno E, Kawashima H, et al. Intestinal Phlebectasias Treated by Endoscopic Injection Sclerotherapy at Double-Balloon Endoscopy. Video Journal and Encyclopedia of GI Endoscopy 2013 June; 1(1): 246-247.
23. Olano C, Machado P, Berrueta J, Irisarri V. Obscure gastrointestinal bleeding due to small-bowel phlebectasias. Endoscopy 2014 May 7; 46: E223-E224.
24. Papanikolau IS, Giannakoulopoulou E, Alder A, Veltzke-Schlieker W. Endoscopic Management of Recurrent Gastrointestinal Bleeding due to Varices in the Terminal Ileum. Dig Endosc 2012 Jan; 24(1): 49.
25. Patel Y, Ramani P, Grier D, et al. Bleeding jejunal phlebectasia in an adolescent: case report. J Pediatr Surg 2008 Feb; 43(2): 405-406.
26. Peoples JB, Kartha R, Sharif S. Multiple Phlebectasia of the Small Intestine. Am Surg 1981 Aug; 47(8): 373-376.
27. Richardson JD, Mcinnis WD, Pestana C. Duodenal Varices. Am Surg 1976 Mar; 42(3): 201-203.
28. Schilling D, Maier M, Kohler B, Wurmel W, Jakob P, Riemann JF. Idiopathic mesenteric varices causing lower gastrointestinal bleeding. Eur J Gastroenterol Hepatol 1996 Feb; 8(2): 177-179.
29. Tang SJ, Zanati S, Dubcenco E, Cirocco M, Christodoulou D, Kandel G, et al. Diagnosis of small-bowel varices by capsule endoscopy. Gastrointest Endosc 2004 Jul; 60(1): 129-135.
30. Vuillemin E, Croquet V, Coumeau D, Ouali L. Idiopathic ileocolonic varices: a rare cause of lower gastrointestinal bleeding. Gastroenterol Clin Biol 2004 Nov; 28(11): 1183-1184.

Cambridge Memorial Hospital has immediate openings for:

- Pediatrician
- Hospitalist
- Hospitalist (with interest in Oncology)
- General Internal Medicine
- Gastroenterology & Hepatology
- Dermatology

We are a 144-bed acute care hospital **undergoing an expansion of our facilities** and **growth in services**. We are affiliated with the Waterloo Campus of the *Michael G. DeGroote School of Medicine*, McMaster University, supporting academic interests of professionals practicing in Cambridge, Ontario and the Region of Waterloo.

Our specialist programs include: Cardiology, Respirology, Gastroenterology, Rheumatology, Hospitalist Medicine, General Surgery, Urology, OBS/GYN, Pediatrics, ENT, Oncology, Orthopedic surgery, Plastic surgery, Neurology, Radiology and Psychiatry. Access to other specialist programs are available within the Waterloo Wellington LHIN.

Cambridge is a family-oriented community of 140,000 in the bustling, high-tech Region of Waterloo. It is conveniently located one hour from Toronto, London, and Hamilton. Our business-friendly environment and appealing lifestyle have made us one of the fastest-growing cities in Canada.

More Information? Connect with:

Nithya Abraham, Medical Administration
Tel: 519-621-2333, ext. 2370; Fax: 519-740-4934
Email: nabraham@cmh.org
Please quote posting # MCMAR19

CAMBRIDGE MEMORIAL HOSPITAL

MCI THE DOCTOR'S OFFICE™

YOUR NEXT STEP IS WITH US

CELEBRATING 30 YEARS 1986 2016

- ✓ Walk-In & Family Practice Opportunities
- ✓ Billing Support To Maximize Your Income
- ✓ Marketing To Build Your Practice
- ✓ Professionally Trained Staff
- ✓ Complete EMR Training
- ✓ 20+ MCI Clinics in Ontario & Alberta

Contact MCI Today!
416 440 4040 EXT 105
practice@mcimed.com

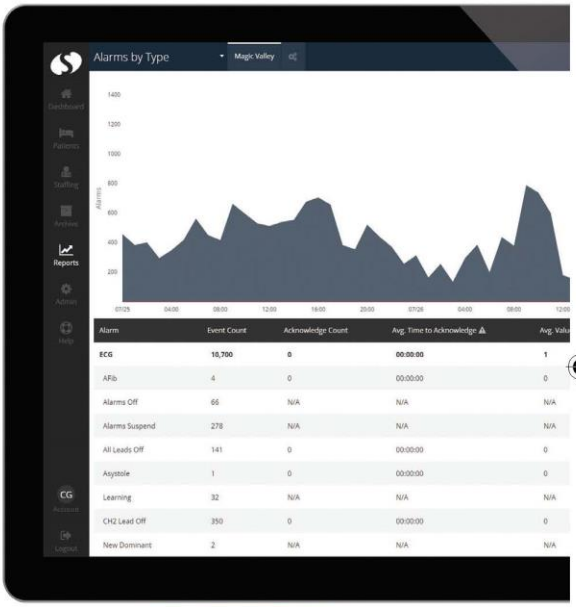
Physician Opportunities Available Online

mcithedoctorsoffice.com

ALARM FATIGUE?
TAKE BACK CONTROL

Spacelabs SafeNSound™ provides a simple, actionable reporting tool designed to help you reduce noise and increase patient safety.

- Review alarm data from previous hours, shifts, days, months, or even years.
- See alarm counts by department or location, and by parameter.
- Access customized reports including alarm events, alarm settings, and user responses.



SPACELABS SAFENSOUND™

Review Article

Multiple sclerosis: Unraveling the neuropathology and nechanisms of neurodegeneration

Samantha Visva[a] and John Paul Oliveria, PhD[b,c]

[a]Faculty of Health Sciences, McMaster University, Hamilton, Canada

[b]School of Medicine, Department of Pathology, Stanford University, Palo Alto, USA

[c]Department of Medicine, Division of Respirology, McMaster University, Hamilton, Canada

Abstract

Multiple Sclerosis (MS) is a debilitating autoimmune disease affecting the central nervous system and has been the focus of intense research for the past 20 years. A better understanding of immune-related pathogenic mechanisms is necessary for the development of: (1) novel methods to monitor disease progression, (2) earlier diagnoses through unveiling new biomarkers, and (3) the invention of more effective and personalized MS treatments therapies. Several disease modifying treatments (e.g., natalizumab, fingolimod and beta interferons) have been approved for MS; however, with no cure, the current treatment paradigm has shifted to the notion of 'no evident disease activity'. While many of these Food and Drug Administration approved MS treatments have been shown to reduce the number of relapses and lesions, the paradox concerning MS treatments, namely the overuse of T cell activation as a target, necessitates the need for identifying entirely new contributors to disease pathology. MS pathogenesis has been associated with many theories, ranging from the release of proinflammatory cytokines from macrophages and microglial cells to B cell-derived demyelinating antibodies. As such, these hypotheses should be considered in addition to the role of T cells when developing novel MS treatment plans and identifying aligning biomarkers. Recently, clinical trials (ClinicalTrials.gov Identifier: NCT00040482, NCT00342134, and NCT00342134) investigating autologous hematopoietic stem cell transplantation have demonstrated success in MS. Future research should focus on identifying non-invasive biomarkers, such as blood concentrations of miRNAs, as an indication of underlying pathology and to aid in early diagnosis, tracking disease progression and identifying more effective and personalized MS treatments.

Keywords: Multiple sclerosis; therapies; pathogenesis

Corresponding author: John Paul Oliveria, oliveria@stanford.edu; olivejp@mcmaster.ca

Introduction

The immune system is a complex network of interacting components including cells, tissues and organs that fight invading microorganisms by maintaining the body's lines of defense.[1] The body's ability to do so is likely attributed to its ability to differentiate between "self" and "non-self", resulting in complex immunological communication.[1] When immune surveillance reveals that foreign cells carry "non-self" markers, a response is activated.[1] Millions of cells, each subset with their own orchestrated functions, signal and send information to each other to further activate inflammatory signaling cascades by producing chemicals, such as cytokines.[1] The body recognizes and responds to non-self markers (antigens) by secreting specific chemicals and activating specialized cells to destroy them[1]. If the body is left undefended, foreign invaders such as bacteria, parasites, fungi and viruses can cause infections, leading to a variety of adverse health effects.[1]

The lymphatic system is organized throughout the body to maintain optimal protection.[1] Lymphocytes are specialized immune cells, and reside in lymphoid organs such as the thymus, bone marrow, spleen and lymph nodes, where they are able to impart immunity.[1] Primary lymphoid organs including the bone marrow and thymus are responsible for the development and maturation of lymphocytes while secondary lymphoid organs, such as lymph nodes, tonsils and the spleen, are involved in generating immune responses and fighting infection by interacting with non-self pathogens.[1,2] The bone marrow gives rise to all lymphocytes and following multiplication, they enter the bloodstream for further specialization into mature lymphocytes.[1,2]

The central nervous system's (CNS) ability to regulate immune and inflammatory responses is dependent on the interactions between brain structures and their microenvironment.[3] Specifically, the blood brain barrier (BBB) is a structure within CNS capillaries composed of tight endothelial junctions that limits access of circulating immune cells, antigen presenting cells (APCs) and inflammatory cytokines to maintain the integrity of the CNS.[3] In a systemic inflammatory response, if these cells and cytokines within the bloodstream were to gain entry into the brain, this could have deleterious consequences. In normal conditions, only a small percentage of immune cells, cytokines and chemokines, such as interleukin (IL)-1, tumor necrosis factor alpha (TNF-α) and IL-6 enter the CNS.[3,4] Immune privilege refers to the features present in the CNS to impede potentially damaging immune reactions, such as the BBB and incompetent APCs.[5] Typically, APCs express costimulatory molecules and exposure to foreign antigens in their activation; however, APC incompetence refers to the lack of MHC and costimulatory molecule expression within CNS macrophage populations, which helps regulate T cell responses.[6]

In many neurodegenerative diseases such as Multiple Sclerosis and Alzheimer's Disease, CNS pathology is accompanied by BBB dysfunction which permits penetration through the BBB and elicits a response by resident brain cells, such as microglia and astrocytes.[3] Neurons in pathological states release inflammatory signals, resulting in activation of oligodendrocytes. Oligodendrocytes, the cells that support myelin production are highly vulnerable to ROS-induced

injury (or other specific molecules) produced by immune reactions due to their structure.[3] Specifically, oligodendrocytes have high concentration of polyunsaturated fatty acids, low anti-oxidative enzyme glutathione concentrations and free radical scavengers which cause lipid peroxidation.[7,8] Immature oligodendrocyte progenitors are even more susceptible to oxidative stress due to higher levels of pro-apoptotic proteins.[8]

This invasion of the BBB resembles typical leukocyte infiltration which involves chemoattraction, adhesion and diapedesis across capillary walls. The entry into brain parenchyma occurs in two steps: (1) migration across the vascular wall and (2) glial limitans.[9] Following migration across endothelial cells in a mature CNS capillary, these invading substances interact with glial limitans, also known as astrocyte foot processes, which participate in tight junction function, contributing to normal vessel structure integrity.[10] Endogenous or exogenous leukocyte sources elicit CNS immune responses that may serve pathological functions in multiple sclerosis (MS), namely the damaged areas called lesions, created by infiltrating macrophages and T cells inflicting damage upon oligodendrocytes, myelin, and their underlying nerves.[9] The role of immune cells in the pathogenesis of MS as well as the standard and potential treatments in the pipeline will be explored in this review.

Multiple sclerosis

Multiple Sclerosis (MS) is a neurodegenerative and chronic inflammatory disease of the grey and white matter in the CNS, characterized by demyelination with relative sparing of axons.[11,12] Specifically, the activation of local macrophages by autoreactive T helper cells (Th1) destroys the insulating layer around nerves called myelin.[11] Myelin allows for the transmission of electrical messages along nerve cells and the disruption of these myelin sheaths slows or stops these impulses, resulting in neurological problems. Grey matter contains neuronal cell bodies, dendrites and terminals which participate in synapses, the site of communication between neurons.[13] As the cell body is vital for neuronal life, grey matter damage primarily includes neuronal death as the cell is unable to support its axon or dendrites.[13] White matter, denoted by its colour, is composed of the axons connecting neurons of grey matter.[14] White matter injuries sever communication between areas of grey matter, which result in the inability to relay information, such as motor or sensory, to muscles or skin.[15] MS is associated with a wide spectrum of disabilities such as motor impairments, sensory deprivation, decreased cognitive function and cerebellar and brainstem dysfunction.[11] The autoimmune pathogenesis of MS involves many immune cell groups, and its pathological mechanisms have been oversimplified in the past with the sole implication Th1 cells in plaque formation and demyelination.[12] However, current research is indicating differently with a focus on B cells and the role of demyelinating antibodies in MS pathology.[12] Specifically, autoreactive B cells infiltrate the CNS, and once expanded, these B cells may produce antibodies that attack myelin.[12] These antibodies can be identified in the CSF of patients and increase with disease progression and the number of active lesions, which may serve as a diagnostic tool.[16] The use of next generation sequencing, a tool

that determines nucleic acid sequences, has allowed for the analyzation of B cell receptors to characterize B cell populations found in MS, which suggests that there is therapeutic potential by targeting B cell subtypes.[16] Evidence for this stems from research evaluating the role of anti-CD20 B cell depleting therapies such as rituximab, ocrelizumab and ofatumumab.[17,18] MS is marked by fluctuating periods of exacerbation and remission, and is characterized by four clinical presentations: relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS).[8]

Pathogenesis

The pathogenesis of MS emphasizes the expansion of autoreactive T cells that cross the BBB, their role in activating microglia, and the demyelinating effect of microglial products.[11] The infiltration of monocytes is made possible by the breakdown of the BBB tight junctions due to reactive oxygen species (ROS).[19] Autoreactive Th1 cells interact with the endothelial cells through cell adhesion molecules (CAMs), which are involved in binding other cells and allow for their trafficking across the BBB).[19] This migration across the BBB increases subsequent permeability for other leukocytes as a result of their initial release of pro-inflammatory cytokines).[19] These Th1cells activate macrophages and microglial cells via IFN-γ, TNF-α or IL-2, which stimulates reactive microglia to express MHC II molecules, highlighting their role in further T cell activation.[11,12] These cytokines also activate transcription factors responsible for Th1 differentiation, such as T-bet and Stat-4, causing cells to differentiate into their Th1 phenotypes.[20] As the primary effector immune cell in the CNS, microglia have phagocytic, antigen presenting and cytokine generation abilities.[21] Activated microglia release proteases, TNF-α, reactive oxygen species (ROS) and metalloproteinases, which damage oligodendrocytes and myelin.[11] ROS-generating enzymes of myeloid cells include myeloperoxidase, xanthine oxidase and NADPH oxidase, which produce ROS, accumulating in sources such as endothelial mitochondria, microglia and astrocytes.[22] These cells are stimulated by inflammation, O^{2+}, H_2O_2, and hydroperoxides which damage endothelial cells by activating kinase pathways and transcription factors, including NF-kB, poly-ADP ribose polymerase.[22] These factors activate inflammatory genes such as ECAMs, MMPs, and iNOS[23]. iNOS recruits NO^{+}- releasing cytokines compromising BBB function by reorganizing the architecture of endothelial TJs including the disruption of zona occuludens-1 and occludin interactions (proteins that help create a scaffold for TJs) and breakdown of extracellular matrix which affects the structural support of TJs.[22,23] As the disease progresses, BBB pathology allows for increasing damage and becomes more vulnerable to ROS effects and immune cell infiltration due to its already weakened state.[22] This highlights the treatment of more advanced cases where the worsened pathology dictates an approach that may be able to deal with the more extensive damage.[24] The combination of these factors contributes to the chronic demyelinated lesions evident in MS.

There are different immune cells involved in demyelination; Figure 1 encompasses the distinct demyelinating roles of T cells, B cells and macrophages. As aforementioned, the

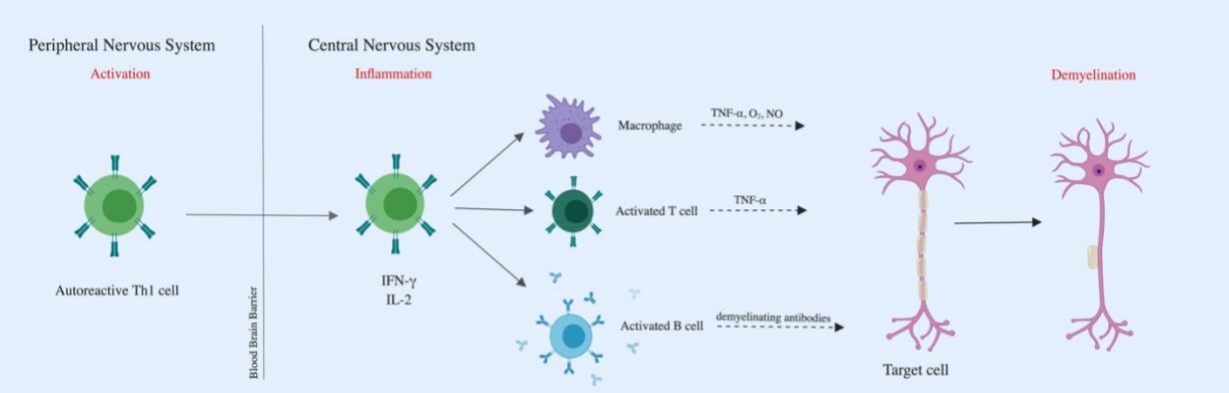


Figure 1: T cell, macrophage and B cell models of MS pathogenesis. Autoreactive T cells penetrate the BBB and secrete Th1 proinflammatory cytokines that stimulate activation of T cells, macrophages and B cells, which induce demyelination through proinflammatory elements, ROS and demyelinating antibodies.

inflammatory response is exacerbated by the toxic mediators of macrophages or ROS in response to T-cell activation. However, the demyelination process is not solely attributed to Th1 responses, as Th17 cells have been recognized in inducing EAE (experimental autoimmune encephalomyelitis), the animal model of an inflammatory demyelinating disease.[25] While autoreactive Th1 cells initiate spinal cord inflammation, myelin-specific Th17 cells promote cell infiltration into brain structures, thus highlighting the unique roles these cells have in allowing inflammatory cells to enter the CNS.[25] The cytokine profile of Th17 cells suggests that these cells promote an inflammatory response by secreting IL-17, a pro-inflammatory cytokine, and

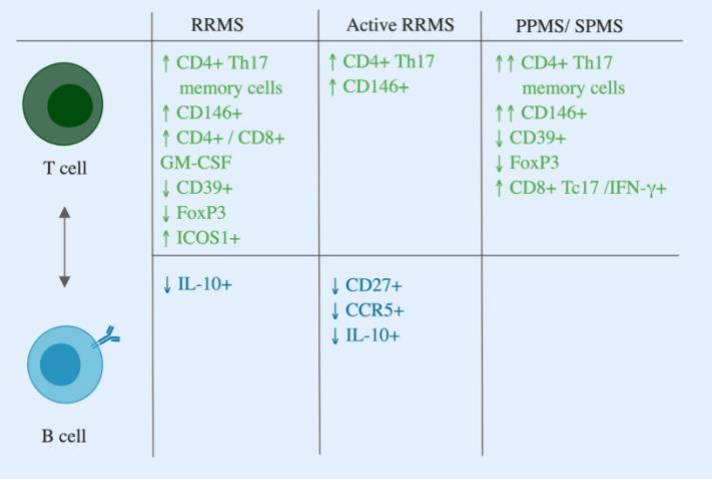


Figure 2: T and B cell marker expression reflects MS disease subtype and disease progression. As disease burden increases, T cells demonstrate increased levels of CD4+ Th17 cells as well as CD146+ expression. However, when RRMS is in the relapsing stage, B cells express decreased levels of CD27 and CCR5. Edited from Jones et al., 2017.

this may be a factor in lesion topology.[25] B cells contribute to the demyelinating process in both antibody-dependent and independent mechanisms. B cells can produce anti-myelin oligodendrocyte glycoprotein antibodies or act in an antibody-independent manner by processing and presenting antigens to T cells, using an EAE model.[25] These antibodies bind myelin antigens which impairs oligodendrocyte metabolism resulting in extensive damage such as disrupted axonal calcium homeostasis, cytoskeleton degradation, axonal transport blockage and the activation of other proteases to further disrupt axonal processes (Table 1).[12,20] As MS disease burden progresses, T and B cells reflect this by their cell surface marker expression, outlined in Figure 2.[26]

Table 1: Summary of MS neurodegenerative disease model and mechanisms, including prevalence, risk factors, disease pathology and standard of care treatments.

Multiple Sclerosis		References
Prevalence	● 4000 new cases of MS diagnosed every year in Canada	[49]
Risk Factors	● Mutations identified in HLA locus and other chromosomes (eg. 10p15, 5p13, and 1p36) ● Pathogens and viral infections may provide an environment to increase susceptibility to MS	[20,29]
Pathology	● MS is associated with demyelination and irreversible acute axonal injury ● Active lesions result in tract degeneration and neuronal atrophy	[12]
Standard of Care Treatment	● FDA approved MS treatments address symptoms such as inflammation ● GA or IFN-β products are delivered subcutaneously or intramuscularly to regulate pro-inflammatory cytokine secretion and T cell activation ● Escalation and induction DMTs mitigate relapse and the formation of new lesions	[29,33]

Demyelination processes between individuals vary and this suggests a heterogenous nature in the progression of MS.[12] Irreparable acute axonal injury is caused by demyelination present in active lesions.[12] Tract degeneration and neuronal atrophy are the cause for MS-associated symptoms, with the severity of axonal loss correlated to the number of toxic mediators (NO, proteases) released by infiltrating macrophages and Th1 cells in active lesions.[12] Affected areas include the optic nerve, cerebrum, brain stem and cerebellum and spinal cord which translate to symptoms such as vision loss, cognitive impairments, sensory and motor deficits and ataxia, illustrated by Figure 3.[27]

Stark comparisons can be drawn between myelin reactive T cells in those with and without MS. In patients with MS, antigen-specific cells are activated, whereas the same cells in

patients without MS are naïve.[20] The chemokine receptors expressed on reactive T cells and the cytokines released are aligned towards a Th1 response and more inflammatory in those with MS.[20]

Complement proteins opsonize oligodendrocyte and myelin membranes via 29,39-cyclic nucleotide 39-phosphodiesterase (CNP) for phagocytosis by microglial membrane receptors, further highlighting their role in MS pathogenesis.[11] Astrocytes typically suppress the phagocytic, antigen presenting, and cytokine producing functions of microglia to support axonal regrowth and stimulate remyelination within the CNS.[11] Upon exposure of IL-4, astrocytes,

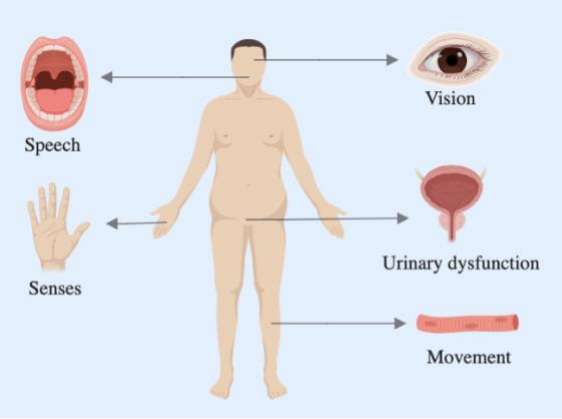


Figure 3: The infiltration into the BBB and its related brain structures translates to symptoms such as vision loss, cognitive impairments, urinary dysfunction and sensory and motor deficits.

which express IL-4 receptors, release neurotrophic factors such as nerve growth factor, glial-cell-line-derived neurotrophic factor and basic fibroblast growth factor (bFGF).[11] Astrocytes also respond to infiltrating immune cells by inducing apoptosis.[11] Other cells present in active lesions that may contribute to the inflammatory response include granulocytes, eosinophils and Th2 cells.[12]

As demonstrated by Figure 4, the infiltration of immune cells across the BBB in degenerative diseases highlights the interaction between microglia and astrocytes, by inhibiting microglial phagocytic properties to propel the neurodegenerative processes.[28] The disease is characterized by increasing neuronal death translating to motor and/or cognitive impairment.[21]

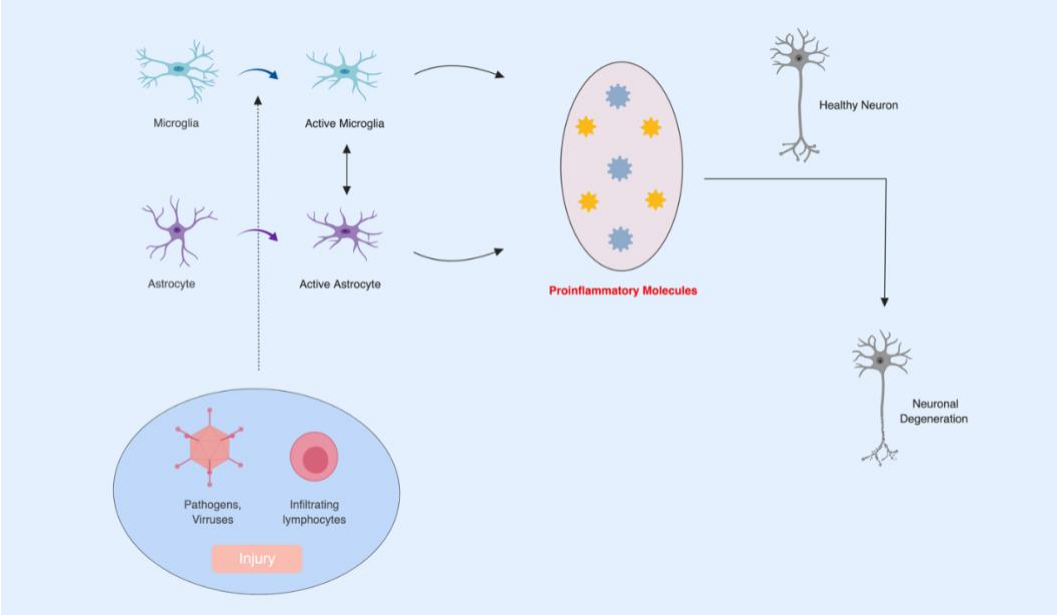


Figure 4: Microglia and astrocytes undergo morphological changes to their activated states following interaction with immune cells that have infiltrated the BBB. These autoreactive cells inflict injury upon the CNS and as such, microglia and astrocytes release proinflammatory signals, such as cytokines, that result in the perpetual mutual activation of these cells. Generally, these cells return to their resting state, however in patients with MS, there is a persistent activation, which triggers downstream cascades, ultimately causing neuronal degeneration.

Etiology

Though there is no distinct trigger leading to the development of MS, genetic and environmental risk factors are postulated to contribute to a person's development of the disease.[20] Identified loci associated with MS include the DR antigens in the HLA locus on chromosome 6p21, specifically the HLA-DRB1*1501-DQB1*0602 haplotype (DR2).[29] Other chromosomes with MS-susceptibility include: 10p15, 5p13, and 1p36.[29] In terms of environmental factors, exposure to vitamin D, a protective factor, as well as infectious agents become increasingly important before the age of 15 in the development of MS.[29] Pathogens and viral infections such as the human herpesvirus type 6, Epstein Barr virus, mycoplasma pneumoniae, upper respiratory tract infections and bacterial urinary tract infections provide an appropriate environment for the development of MS by stimulating toll-like receptors (Table 1).[20, 29] Toll-like receptors (TLRs) expressed on immune cells, such as microglia, recognize pathogen-associated molecular patterns on pathogens, causing them to produce proinflammatory cytokines.[30] This results in the reactivation of myelin-acting autoreactive T cells in the CNS.[29] The TLR signalling pathway plays a role in oxidative stress, including the production of ROS.[29] The multifactorial MS model suggests that all of these factors contribute to oligodendrocyte and neuronal cell death.

Diagnosis

Due to the spectrum of symptoms experienced with cases of MS, there is great diversity in the presentation of MS across individuals. Some individuals may seek out ophthalmologists and orthopedic surgeons, who will then refer them to a neurologist if MS is suspected.[31] CIS is the first presentation of an individual's neurological episode, caused by localized inflammation and demyelination or damage incurred across brain structures.[31,32] CIS presentation may include acute unilateral optic neuritis (inflammation of the optic nerve), partial myelitis (inflammation of the spinal cord) or brainstem syndrome, including symptoms such as difficulty breathing, speaking and swallowing.[31] However, the onset of MS may be slowly progressive, with neurological symptoms that evolve over months.[31] The diagnosis of MS is made by assessing neurological symptoms characteristic of MS, such as sensory or motor impairments, and CNS lesions (this combination is illustrated in Figure 5).[31] As per the 2016 European Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network, MRIs can help determine the extent of histopathological MS features, such as inflammation, the state of myelination, gliosis, axonal loss and presentation of CSF oligoclonal bands.[32] Spinal cord MRIs may be recommended if the individual has myelopathy (spinal cord disease) or inconclusive MRI brain findings.[31]

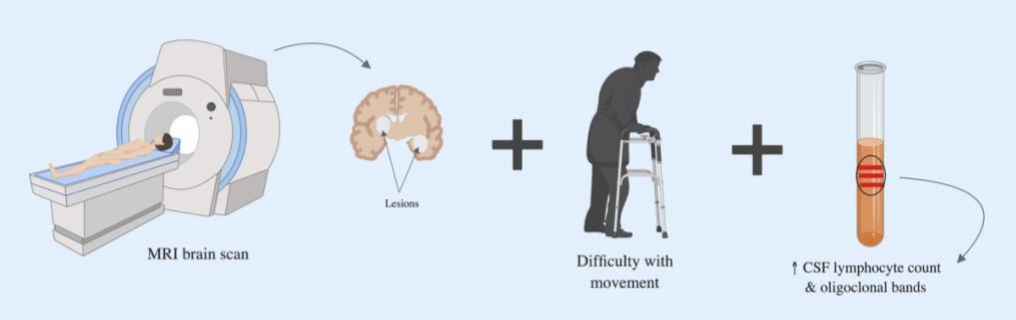


Figure 5: Diagnosis of MS is made by evaluating three factors: neurological symptoms (ex. motor impairment), the presence of CNS lesions on MRI brain scans and laboratory testing (CSF oligoclonal bands).

Current guidelines for an MS diagnosis are the 2017 McDonald criteria, which emphasizes the distinction between typical clinically isolated syndrome (CIS) and MS, where it is only applied to individuals who already have a greater likelihood of having MS, as CIS usually predates the other forms of MS.[32] The combination of patient history, physical examination and results of imaging and laboratory testing are necessary to make a reliable MS diagnosis.[32] As with other diagnostic tools, the trade-off between sensitivity and specificity exists with new considerations implemented in the 2017 revision in order to improve these scores.[32] Additional criteria as per the 2017 revisions include: the requirement of one periventricular lesion, the inclusion of both symptomatic and asymptomatic lesions in order to better understand the dissemination of lesions across space and time and the use of cortical lesions in the determination of MS (this was previously neglected as standard MRIs have limited ability to

illustrate cortical lesions).[32] The difference between the 2017 revision and prior versions illustrates the importance of CSF analysis and considering possible differential diagnosis.[32] MRIs can be used to confirm the diagnosis, however, in some cases, further testing, such as a CSF examination and neurophysical testing may be warranted.[31] CSF findings may reveal an increased white cell count, mainly lymphocytes and the presence of oligoclonal bands.[32] Other conditions that can be mistaken for MS include acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica spectrum disorder (NMOSD).[31] The association between aquaporin-4 IgG levels and NMOSD, has confirmed the difference between MS and NMOSD.[31] As clinical, imaging and laboratory testing of ADEM and MS overlap, the additional requirement of encephalopathy (altered level of consciousness and cognitive deficits) is necessary in differentiating ADEM and MS.[31]

The MRI criterion provides different recommendations for the diagnosis of RRMS and PPMS. RRMS diagnoses require evidence of dissemination in space with >1 T2 lesions in at least two of 4 brain areas including periventricular, juxtacortical, infratentorial and spinal cord regions.[31] PPMS requires dissemination in space with a ≥1 T2 brain lesions in at least one of three sites including periventricular, juxtacortical and infratentorial regions and ≥2 T2 spinal cord lesions.[31] As T2 lesion loads are lower in PPMS, CSF may also be required, with positive results requiring ≥2 OCBs and/or elevated IgG levels.[31]

Standard of Care Treatment

Current treatments address MS symptoms and inflammation but are unable to reverse the immune-mediated damage.[29] The FDA approved IFN-beta products are delivered subcutaneously or intramuscularly and are recombinantly produced in *E. coli* bacteria or ovarian hamster cells.[29] This treatment has been used for over 20 years and is used to control the secretion of pro-inflammatory cytokines and T cell activation (Table 1).[29]

Currently there are 14 escalation and induction disease-modifying therapies (DMT) which serve to reduce relapse and formation of new lesions, characterized by nerve damage, but are unable to "cure" the disease.[33] Traditional first line therapies, such as glatiramer acetate (GA) and IFN-β, have been used for two decades, and now prompt research into pre-treatment predictors to optimize individual prognosis and treatment.[33] DMTs differ in administration, mechanistic profiles and side effect, but also vary in responsiveness between individuals.[33,34] The heterogeneity in severity and unpredictability in treatment response require the identification of individualized biological markers to guide treatment decisions with the greatest promise in responsiveness (Table 1).[33]

Clinicians use a trial and error approach but prescribing non optimal treatments impedes the critical treatment window to prevent the transition to secondary progressive MS.[33] Genetic biomarkers will inform clinicians of a patient's response to a given treatment using sequence variation analysis.[33] By identifying polymorphisms expressed in patients with MS, pharmacogenomics evaluates how *a priori* markers predict one's most safe and effective

treatment.[33] As suggested by the literature, future directions for MS treatment requires the adoption of an entirely new approach. This approach to MS treatment is the defined target of no evident disease activity (NEDA), which indicates no relapse, disability progression and MRI activity (MS lesions).[35] An early, more aggressive approach in advanced MS treatments, refocuses expectations to preserve reserve neuronal capacity.[35] Using the length-dependent axonopathy hypothesis, MS progression initiates at pathways with the longest axons and harnessing neuronal systems with reserve function may promote recovery.[35] Combination therapies in advanced MS employs different classes of MS treatments, such as anti-inflammatory therapies, those that target specific innate or adaptive immune mechanisms (activated glia, B cells or T cells), therapeutic monoclonal antibodies and neuroprotective or remyelination therapy.[35]

With no cure, MS patients continue to experience worsening neurological function, uncontrolled clinical symptoms, and staggered periods of remission and as such, the prognosis of MS focuses on quality of life and disability, highlighted in Figure 6.

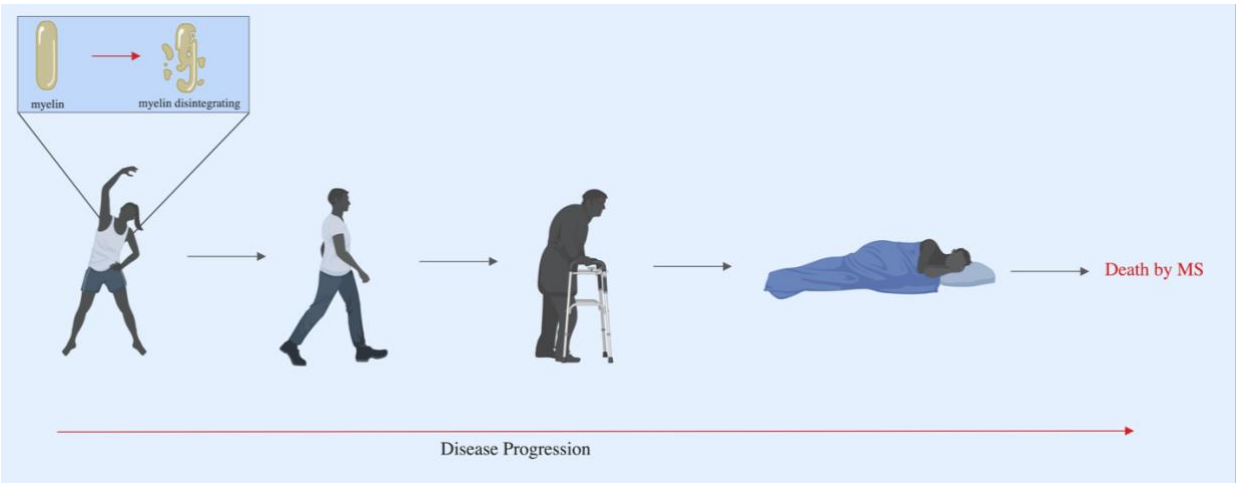


Figure 6: The expanded disability status scale quantifies the disability experienced by patients with MS. As the disease progresses, individuals may transition from no disability to minimal signs of MS, moderate disability in one system or mild disability up to 4 systems with no impairments in walking. As demyelination and the immune cell load becomes too great, this translates to increased motor deficits, with the inability to walk, and may result in MS-related death.

Discussion

Leading research ideologies concerning MS at this time are rooted in investigating better methods to diagnose and treat the disease, including discovering biomarkers, placing an emphasis on training physicians and developing novel treatments.

As the McDonald criteria was based on the data accumulated from academic MS speciality centers, further validation of this criteria is needed in diverse populations without typical presentation of CIS, such as investigating pediatric and late-onset MS patients with

comorbidities in primary practice settings.[32] The 2016 MAGNIMS Criteria will also need to be further validated, and improved by implementing a MRI feature to determine the chronicity of lesions during a patient's first assessment.[32] Increasing field strength imaging may serve to be more sensitive in detecting lesions and distinguishing MS lesions from other conditions, however, more research is needed to determine its efficacy and limitations.[32] With a greater emphasis on precision medicine and advanced technology, MS diagnostic tools will need to be further validated as there is currently no test that can solely diagnose MS.[32]

Biomarkers can aid in early diagnosis, tracking disease progression and identifying effective PD treatments. While there is a lack of clinically validated diagnostic biomarkers, ongoing research is investigating potential biomarkers to support MS treatment.[32] Due to the many targets that have been widely implicated in MS pathogenesis, there is great heterogeneity in the pathogenic mechanisms for the disease which remains widely unknown and to address this, a focus on affected proteins and genes may be beneficial. Screening miRNAs up or downregulated may reveal the underlying pathology of MS, the transition from CIS to MS and medication effects.[36] The stable nature of miRNAs makes the detection of circulating miRs in biofluids simple with methods such as qt-PCR, miRNA array analysis, or next generation sequencing.[36] Following (disease modifying treatment), miR-150 levels were altered in a disease-specific manner.[36] miR 128-3p and miR 191-5p were upregulated in patients with primary progressive MS with differential miR 128-3p levels in comparison to those with secondary progressive MS.[37] miR-128 was upregulated in naive CD4+ T cells in three forms of MS: relapsing-remitting, primary and secondary progressive.[37] MiR-128 suppresses Th2 cell differentiation, promotes the production of Th1 proinflammatory mediators and is involved in the p53, ErbB and TCR signalling pathways, all of which are implicated in MS pathology.[37] MiR 191-5p, involved in cellular differentiation and development, was upregulated in both forms of progressive MS but was downregulated in RRMS patients treated with natalizumab.[37]

Inflammasome signalling proteins also represent potential in reflecting MS pathology.[38] An inflammasome is a multiprotein complex involved in the activation of inflammatory responses and secretion of cytokines such as IL-1β and IL-18. In EAE, IL-1β contributes to the pathogenesis of the disease, however in humans, there is conflicting data with regards to their contribution.[38] Specifically, Caspase-1, apoptosis-associated speck-like protein (ASC) and IL-18 were elevated in the serum of MS patients, with ASC (AUC: 0.9448, CI: 0.9032-0.9864) and caspase-1 (AUC: 0.848, CI: 0.703-0.9929) as the most promising serum biomarkers.[38] The cut-off used for ASC was 352.6 pg/ml with 84% sensitivity and 90% specificity, while the Caspase-1 cut-off was 1.302 pg/ml with 89% sensitivity and 56% specificity.[38] Increasing the sensitivity and specificity compromised the value of the other measure. ASC acted in a dose-responsive manner, where protein levels increased with greater severity, with an AUC of 0.7596 (CI: 0.5437-0.9756).[38] As such, ASC may be a promising biomarker in MS, however, the prognostic potential of these different biomarkers needs to be further studied with regards to this line of research (Figure 7). More studies with larger sample sizes will aid in determining cut-offs to

optimize sensitivity and specificity when using biomarkers levels as a diagnostic tool in conjunction with physical examinations and imaging.

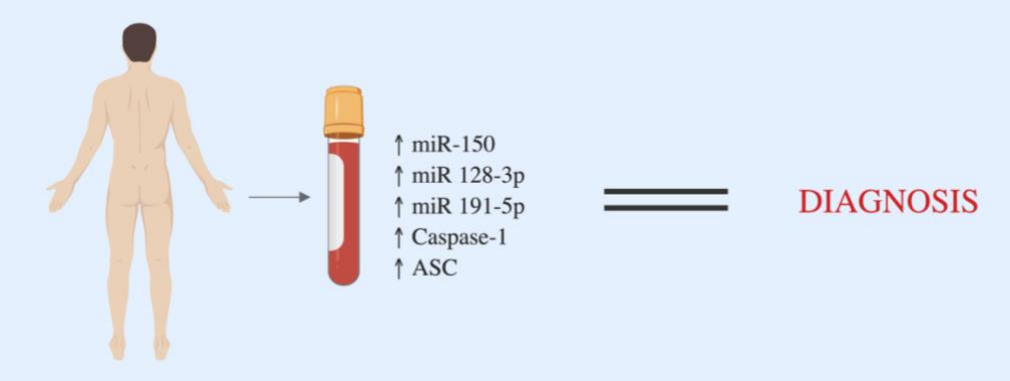


Figure 7: Non-invasive blood biomarkers may serve as a diagnostic tool in conjunction with other tests. Micro-RNA and inflammasome signalling proteins have been observed to be elevated in the serum of patients with MS, however, further tests with larger sample sizes are needed to determine their diagnostic and prognostic potential.

In the past 15 years, great strides have been made to improving the care of MS patients by highlighting the role of earlier individualized treatment plans to prevent long-term irreversible damage.[39] However, while FDA-approved treatments try to slow the progression of the disease or control symptoms experienced by MS patients, these medications are not completely effective.[40] Recently, a greater emphasis has been placed on the merits of medical marijuana in reducing patient-reported symptoms.[40] The only alternative medicine intervention with strong evidence is cannabinoids, where nabiximols, oral cannabis extract and synthetic tetrahydrocannabinol were effective in reducing spasticity and centralized pain.[40] However, the association between cannabis use and risk of schizophrenia and other cardiovascular conditions needs to be considered. As marijuana is now legal in many jurisdictions, adequate education to patients is becoming increasingly important.[40] Spasticity inflicts over 85% of patients with MS, with 17% of patients experiencing severe spasticity. Over 2/3 of patients experience MS-related pain that greatly interferes with their lives.[40] This pain manifests itself in the form of headaches, neuropathic arm or leg pain, back pain and painful spasms by CB1 receptors in the brain and peripheral nerves which process pain.[40]

DMTs are the standard approach in treating MS, however future research is needed to improve physician decision-making with regards to administering DMTs.[41] Areas for future research include: effects of DMT-related outcomes beyond trial outcomes to be better informed of the generalizability of these treatments; subpopulation DMT efficacy to identify optimal treatments for specific groups; long-term effects of using high-potency DMTs early in disease course, changing DMTs or discontinuation; and differences in DMTs for MS and CIS.[41] While DMTs have become integrated into the treatment of MS patients, there are still many questions remaining regarding treatment variation that can be addressed with pragmatic clinical trials.[41] For instance, siponimod has recently been recognized as one of the first DMTs that may be able

to slow the progression of SPMS.[42] Siponimod is a DMT that inhibits the entry of lymphocytes from lymph nodes into the BBB by acting on a selective sphingosine-1-phosphate receptor.[42] The EXPAND phase 3 clinical trial identified a 21% risk reduction of disability in a 3-month time period in patients with SPMS.[42] It has a similar safety profile to other sphingosine-1-phosphate receptor modulators and patients were exposed to the drug for 18 months.[42] Younger patients with greater disease burden, less disability and shorter disease duration were more likely to benefit from siponimod treatment.[42] Perhaps, the use of this drug will be restricted to specific patient populations, however, more studies are needed to evaluate the optimal subpopulation.

Novel treatments are constantly being developed and these represent new opportunities to treat MS. With a greater understanding of the mechanisms involved in MS, many researchers are trying to target specific pathways. For instance, hematopoietic stem cell transplantation (HSCT) has been used primarily as a cancer therapy but has garnered attention in its applicability to MS. Autologous HSCT (aHSCT) has been used in phase I and II trials in patients with advanced MS that have exhausted their DMT options.[43] The risk inherently associated with this therapy only makes it suitable for aggressive forms of MS.[43-47] AHSCT depletes autoreactive cells, such as Th17 cells and mucosal-associated invariant T cells, through the conditioning regimen and anti-thymocyte globulin (ATG).[43] Immune reconstitution allows for the expansion of diverse and specific CD8+ and CD4+ T cells, with B cells undergoing a similar process to reinstate immunological tolerance.[43] These clinical trials and case series have demonstrated efficacy and safety in IV administration of autologous bone-marrow derived HSCs in MS.[43-47] There are many more clinical trials being conducted that focus on different signalling pathways and this may also contribute to the personalized MS treatment paradigm.

Ibudilast, a phosphodiesterase inhibitor, suppresses the inflammatory pathway by acting on cell signalling molecules such as IL-1β, TNF-α, and IL-6.[42] The drug was tested in phase 2 SPRINT-MS randomised trials with 255 progressive MS patients where it reduced the rate of brain atrophy by 48% compared to a placebo.[42] This drug may serve as a promising therapy for another reason, namely its use for drug repurposing, which is the application of a drug that has already been developed for another condition.[42] Ibudilast is used in Japan and Korea to treat asthma and cerebrovascular disorders.[42] This is an interesting realm to explore in future studies as it may provide more opportunities for MS treatment.

Another approach in MS treatment is integrating formal risk management and decision-making training in medical schools and scientific institutions.[48] It has been suggested that clinicians have limited training in decision-making and risk management, reflected by therapeutic inertia (TI).[48] TI is the lack of initiating and intensifying treatment when therapeutic goals are unmet, leading to suboptimal treatment decisions, poor clinical outcomes and greater patient disability.[48] Studies suggest that 50-70% of clinicians do not intensify therapy when it is indicated by guidelines.[48] This may be partially due to *default bias* where clinicians continue to use options selected by others despite the availability of others.[48] This may contribute to the resistance in escalating therapy.[48] However, this may have also be caused by uncertainty of

relapse, insurance barriers, etc.[48] As such, being aware of one's biases and developing educational interventions may mitigate errors and optimize therapy.

Conclusions

The immune system plays a significant role in the neurodegenerative disease progression of MS and propelling neuroinflammation via pro-inflammatory cytokines. A pathological hallmark of MS is a dysfunctional BBB, allowing neuronal and peripherally derived cells, such as B cells, autoreactive T cells and activated microglia, to initiate inflammatory processes and contribute to disease pathogenesis. Oligodendrocytes are fundamental in the protection of the central nervous system, however, during disease processes, namely the demyelination of neurons and neuronal injury propelled by cytokines and signalling molecules such as IFN-γ, TNF-α, ROS, and proteases. As such, the environment exacerbates disease burden through the secretion of proinflammatory cytokines, further propelling neural degeneration. These powerful signalling mechanisms cause extensive damage, illustrated by symptoms reflecting nerve damage, across different sense modalities such as vision and sensory impairments. The functional impact that this has on individuals is profound and as such, controlling MS remains paramount. Future directions involve identifying minimally invasive disease-specific biomarkers, new diagnostic tools, and developing new treatments. Blood biomarker concentrations may inform potential MS biomarkers and aid in the unique treatment model of MS in which targeting these biomarkers may alleviate disease severity. As there were recent revisions in the McDonald criteria, this data must be further tested in populations to evaluate its sensitivity and specificity, but the development of more sensitive imaging would better distinguish MS lesions from other hyperintensities. Clinical trials are being conducted concerning the development of novel treatments, and in 2018 alone, there has been ground-breaking advancements in this field. These treatments have been informed by expanding our understanding immune cell involvement in MS and exploring untraditional methods of managing MS. These results suggest that the future holds great promise with research being conducted concerning the availability of biomarkers to aid in MS diagnosis and tailored treatments to manage disease progression.

References

1. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology. 2018 Sep;14(2):49.
2. Mak TW, Saunders ME, Jett BD. Components of the immune system. In: Mak TW, Saunders ME, Jett BD. Primer to the immune response. 2nd ed. Newnes; 2013 Dec 23; p. 21-54.
3. Aloisi F. The role of microglia and astrocytes in CNS immune surveillance and immunopathology. The Functional Roles of Glial Cells in Health and Disease. 1999: 123-33. Springer, Boston, MA.

4. Rezai-Zadeh K, Gate D, Town T. CNS infiltration of peripheral immune cells: D-Day for neurodegenerative disease?. Journal of Neuroimmune Pharmacology. 2009 Dec 1;4(4):462-75.
5. Galea I, Bechmann I, Perry VH. What is immune privilege (not)?. Trends in Immunology. 2007 Jan 1;28(1):12-8.
6. Carson MJ, Doose JM, Melchior B, Schmid CD, Ploix CC. CNS immune privilege: hiding in plain sight. Immunological reviews. 2006 Oct;213(1):48-65.
7. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. Acta neuropathologica. 2010 Jan 1;119(1):37-53.
8. Van Horssen J, Witte ME, Schreibelt G et al. Radical changes in multiple sclerosis pathogenesis. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2011 Feb 1;1812(2):141-50.
9. Rezai-Zadeh K, Gate D, Town T. CNS infiltration of peripheral immune cells: D-Day for neurodegenerative disease?. Journal of Neuroimmune Pharmacology. 2009 Dec 1;4(4):462-75.
10. Bonkowski D, Katyshev V, Balabanov RD, Borisov A, Dore-Duffy P. The CNS microvascular pericyte: pericyte-astrocyte crosstalk in the regulation of tissue survival. Fluids and barriers of the CNS. 2011 Dec;8(1):8.
11. Minagar A, Shapshak P, Fujimura R et al. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. Journal of the Neurological Sciences. 2002 Oct 15;202(1-2):13-23.
12. Lassmann H, Brück W, Lucchinetti C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. Trends in Molecular Medicine. 2001 Mar 1;7(3):115-21.
13. Dixon KC. Cytochemistry of cerebral grey matter. Quarterly journal of experimental physiology and cognate medical sciences. 1954 Aug 16;39(3):129-51.
14. Mori S, Wakana S, Van Zijl PC, Nagae-Poetscher LM. MRI atlas of human white matter. Elsevier; 2005 May 11.
15. Lassmann H. Axonal and neuronal pathology in multiple sclerosis: what have we learnt from animal models. Experimental neurology. 2010 Sep 1;225(1):2-8.
16. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nature Reviews Immunology. 2015 Sep;15(9):545.
17. von Büdingen HC, Palanichamy A, Lehmann-Horn K, Michel BA, Zamvil SS. Update on the autoimmune pathology of multiple sclerosis: B-cells as disease-drivers and therapeutic targets. European neurology. 2015;73(3-4):238-46.
18. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. The Lancet Neurology. 2015 Apr 1;14(4):406-19.
19. Larochelle C, Alvarez JI, Prat A. How do immune cells overcome the blood–brain barrier in multiple sclerosis?. FEBS letters. 2011 Dec 1;585(23):3770-80.

20. Frohman EM, Racke MK, Raine CS. Multiple sclerosis—the plaque and its pathogenesis. New England Journal of Medicine. 2006 Mar 2;354(9):942-55.
21. Liu Z, Zhou T, Ziegler AC et al. Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. Oxidative Medicine and Cellular Longevity. 2017;2017.
22. Freeman LR, Keller JN. Oxidative stress and cerebral endothelial cells: regulation of the blood–brain-barrier and antioxidant based interventions. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2012 May 1;1822(5):822-9.
23. Ortiz GG, Pacheco-Moisés FP, Macías-Islas MÁ, Flores-Alvarado LJ, Mireles-Ramírez MA, González-Renovato ED, Hernández-Navarro VE, Sánchez-López AL, Alatorre-Jiménez MA. Role of the blood–brain barrier in multiple sclerosis. Archives of medical research. 2014 Nov 1;45(8):687-97.
24. Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. Journal of neurology. 2004 Mar 1;251(3):261-8.
25. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. The Lancet Neurology. 2015 Apr 1;14(4):406-19.
26. Jones AP, Kermode AG, Lucas RM, Carroll WM, Nolan D, Hart PH. Circulating immune cells in multiple sclerosis. Clinical & Experimental Immunology. 2017 Feb;187(2):193-203.
27. Johnston Jr RB, Joy JE, editors. Multiple sclerosis: current status and strategies for the future. National Academies Press; 2001 Aug 10.
28. Minagar A, Shapshak P, Fujimura R et al. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. Journal of the Neurological Sciences. 2002 Oct 15;202(1-2):13-23.
29. Loma I, Heyman R. Multiple sclerosis: pathogenesis and treatment. Current Neuropharmacology. 2011 Sep 1;9(3):409-16.
30. Racke MK, Drew PD. Toll-like receptors in multiple sclerosis. InToll-like Receptors: Roles in Infection and Neuropathology 2009 (pp. 155-168). Springer, Berlin, Heidelberg.
31. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. The Lancet. 2017 Apr 1;389(10076):1336-46.
32. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018 Feb 1;17(2):162-73.
33. Grossman I, Knappertz V, Laifenfeld D et al. Pharmacogenomics strategies to optimize treatments for multiple sclerosis: Insights from clinical research. Progress in Neurobiology. 2017 May 1;152:114-30.
34. Fox RJ. Tissue Markers for Acute Multiple Sclerosis Treatment Response—A Step Toward Personalized Medicine. JAMA Neurology. 2018 Apr 1;75(4):406-7.

35. Giovannoni G. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. Current Opinion in Neurology. 2018 Jun 1;31(3):233-43.
36. Harris VK, Tuddenham JF, Sadiq SA. Biomarkers of multiple sclerosis: current findings. Degenerative Neurological and Neuromuscular Disease. 2017;7:19.
37. Vistbakka J, Elovaara I, Lehtimäki T et al. Circulating microRNAs as biomarkers in progressive multiple sclerosis. Multiple Sclerosis Journal. 2017 Mar;23(3):403-12.
38. Keane RW, Dietrich WD, de Rivero Vaccari JP. Inflammasome proteins as biomarkers of multiple sclerosis. Frontiers in neurology. 2018 Mar 19;9:135.
39. Romeo MA, Martinelli V, Dalla Costa G, Colombo B, De Feo D, Esposito F, Ferrè L, Guaschino C, Guerrieri S, Liberatore G, Martinelli Boneschi F. Assessing the role of innovative therapeutic paradigm on multiple sclerosis treatment response. Acta Neurologica Scandinavica. 2018 Nov;138(5):447-53.
40. Rice J, Cameron M. Cannabinoids for treatment of MS symptoms: state of the evidence. Current Neurology and Neuroscience Reports. 2018 Aug 1;18(8):50.
41. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BA, Gronseth GS, Haboubi M, Halper J, Hosey JP, Jones DE, Lisak R. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018 Apr 24;90(17):777-88.
42. Ciccarelli O. Multiple sclerosis in 2018: new therapies and biomarkers. The Lancet Neurology. 2019 Jan 1;18(1):10-2.
43. Mancardi G, Sormani MP, Muraro PA et al. Intense immunosuppression followed by autologous haematopoietic stem cell transplantation as a therapeutic strategy in aggressive forms of multiple sclerosis. Multiple Sclerosis Journal. 2018 Mar;24(3):245-55.
44. Cohen JA, Imrey PB, Planchon SM et al. Pilot trial of intravenous autologous culture-expanded mesenchymal stem cell transplantation in multiple sclerosis. Multiple Sclerosis Journal. 2018 Apr;24(4):501-11.
45. Rebillard R, Haddad E, Perreault S et al. A case of aggressive pediatric multiple sclerosis successfully treated with an autologous hematopoietic stem cell transplant. Cytotherapy. 2018 May 1;20(5):S117.
46. Bose G, Atkins HL, Bowman M et al. Autologous hematopoietic stem cell transplantation improves fatigue in multiple sclerosis. Multiple Sclerosis Journal. 2018 Sep 25:1352458518802544.
47. Comini-Frota ER, Marques BC, Torres C et al. No evidence of disease activity after five years of autologous hematopoietic stem cell therapy for multiple sclerosis: detailed report of five patients. Journal of Neuroscience and Neuropsychology. 2018;2:201.
48. Saposnik G, Montalban X. Therapeutic inertia in the new landscape of multiple sclerosis care. Frontiers in neurology. 2018 Mar 20;9:174.

49. Wong S, Ramage-Morin P, Gilmour H. Multiple sclerosis: prevalence and impact. Catalogue No. 82-003-X. [Internet]. Retrieved November 15, 2018 from: https://www150.statcan.gc.ca/n1/pub/82-003-x/2018001/article/54902-eng.htm

Review Article

Are atypical antipsychotics the least detrimental alternative?

Holly Breton

Department of Medicine, McMaster University, Hamilton, Canada

Abstract

Antipsychotics are typically used for the treatment of schizophrenia, bipolar disorder, and recently, treatment resistant major depressive disorder. A significant, and very concerning, side effect present with first generation antipsychotics is extrapyramidal symptoms, which are disorders of movement. With the advent of atypical antipsychotics, also known as second-generation antipsychotics, these symptoms are purported to be much less frequent and pronounced than they were with the first generation medications. Numerous hypotheses have been proposed as to why atypical antipsychotics produce fewer extrapyramidal symptoms compared to first generation antipsychotics, which this paper will review. Unfortunately, despite the fact that atypicals have reduced extrapyramidal symptoms in those taking antipsychotics, extrapyramidal symptoms are still an unpleasant and potentially dangerous side effect, which can be difficult to detect, and difficult, or even impossible, to treat. Additionally, atypical antipsychotics result in other potentially very serious side effects, specifically and most commonly, metabolic syndrome, which can decrease life expectancy significantly. However, metabolic syndrome, unlike extrapyramidal symptoms, may be preventable in highly motivated and well-supported patients. Thus, this paper concludes that the benefits of the atypical antipsychotics (reduced extrapyramidal symptoms) outweigh the potential risks for the majority of patients.

Keywords: antipsychotics, extrapyramidal symptoms, metabolic syndrome

Corresponding author: holly.breton@medportal.ca

Introduction

Antipsychotic medications are first line recommendation for the treatment of psychotic disorders (i.e. schizophrenia) and bipolar disorder. [1, 2] The advent of such antipsychotic medications has had a huge influence on the management of mental illness. The addition of chlorpromazine, the first antipsychotic drug on medical formularies, resulted in a major decrease in the number of institutionalized individuals, thereby improving quality of life for those with serious psychopathology.[3] However, despite numerous benefits, antipsychotics are associated with potentially unpleasant and severe side effects. For example, extrapyramidal symptoms (EPS), which are disorders of movement, may appear hours, months, or even years after the initiation of the medication.[4] Until as recently as the 1980s, it was incorrectly believed that EPS were a necessary aspect of the treatment of psychosis with antipsychotics; in fact, physicians historically used the development of EPS to gauge efficacy of new therapeutic targets.[5]

The introduction of the second generation of antipsychotics (atypical antipsychotics) has generally resulted in a reduction of EPS.[6] However, while it is commonly believed EPS do not occur with the atypical antipsychotics, EPS remain a prominent side effect that must be carefully monitored for over the course of therapy with both first and second generation antipsychotics. This remains the case, despite the fact that atypical antipsychotics differ from first generation (typical) antipsychotics in their mechanisms of action, pharmacokinetics, and pharmacodynamics, as well as in their side effect profile. Within the atypicals as well, there are many pharmacological differences which necessitate categorization5. Some argue however that the reduction in EPS is not truly due to such differences, but rather that in the past, the EPS associated with first generation antipsychotics were a result of over-dosing, and not medication type. As such, they propose that the advantage of the atypicals is their relatively lower effective dosing requirements.[5]

Despite the benefit of fewer EPS, due either to different mechanisms or lower dosing requirements, it is also important to consider that atypical antipsychotics have other serious, potentially life threatening side effects, including metabolic syndrome.[7] This paper will review the current literature pertaining to side effects of atypical antipsychotics, including EPS and metabolic syndrome. Specifically, this paper will focus on the proposed hypotheses regarding the mechanisms by which atypical antipsychotics are associated with fewer EPS. This paper will also attempt to determine whether the literature suggests that the atypical antipsychotics are actually superior to the first generation antipsychotics, considering underlying biological, psychological, and social contexts of affected patient populations.

Atypical antipsychotics

Atypical antipsychotics are a class of medication that are characterized by their supposed reduced risk of EPS at therapeutic doses, a lack of prolactin elevation, and, a significant reduction in positive and negative schizophrenia symptoms.[8] Medications that are classified as

atypical antipsychotics include Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, and Brexpiprazole.[6] These drugs vary greatly in their mechanisms of action, pharmacokinetics, and pharmacodynamics, making it difficult to understand what common factor links them together.[6] Exemplifying the vast differences between the various atypical antipsychotics, Clozapine, the first of this class, has a high affinity for a number of receptors, including, dopaminergic, serotonergic, histaminergic, and muscarinic receptors, with selectively in the mesolimbic area.[8] Other atypical antipsychotics, such as Risperidone, Olanzapine, Quetiapine, and Ziprasidone mainly act as dopaminergic D2 and serotonergic 5-HT antagonists. Aripiprazole, on the other hand, is a D2 partial agonist.[7] Furthermore, the half-lives of the atypical antipsychotic drugs vary widely; Clozapine has a half-life of 5 to 16 hours, whereas Aripiprazole has a half-life of 75 to 146 hours.[7,8,9] There are even differences in the routes of administration among the atypicals, with some medications being available only in oral formulations (e.g. Clozapine), while others can also be administered intra-muscularly (i.e. Ziprasidone and Aripiprazole). Others including Risperidone and Aripiprazole are also available in long-acting injectable preparations.[7] Finally, the various drugs differ in efficacy for various clinical presentations.[8] For instance, Clozapine is generally effective for treatment resistant schizophrenia, whereas Risperidone is recommended for acute psychosis.[7] Furthermore, some of the atypicals are recommended for the treatment of bipolar mania (e.g. Clozapine, Olanzapine, Ziprasidone), where others are also effective in the treatment of bipolar depression (e.g. Quetiapine). Others have selectivity for the bipolar maintenance phase (e.g. Olanzapine, Aripiprazole, Quetiapine, Risperidone).[7] Furthermore, Risperidone is effective in the treatment of adolescents with psychosis, Aripiprazole is useful as an adjunctive treatment for Major Depressive Disorder, and Quetiapine has been approved as both monotherapy and adjunctive treatment of Major Depressive Disorder.[7,10] Given the wide clinical applications of the various atypical antipsychotics, it is important that we obtain a strong understanding of the potential serious side effects of these medications, including EPS.

Extrapyramidal symptoms

Extrapyramidal symptoms are muscular spasms and other movement difficulties often caused by medications such as antipsychotics. EPS include: parkinsonian motor signs, akathisia (feelings of motor restlessness), dystonia (sustained muscular contraction), and dyskinesia (irregular jerky movements).[4] Some of the characteristics of EPS are similar to those seen in Parkinson's Disease, and thus, it is thought that EPS are associated with a reduction in dopamine signaling, specifically, a D2 blockade in the nigrostriatal region.[11] EPS can be severe and unpleasant, and may interfere with medication adherence.[12] Additionally, these symptoms can be acute (develop within hours or days of taking the medication) or tardive (develop only after chronic exposure to antipsychotics).[4] Due to the different mechanisms of action of the various atypical antipsychotics, these drugs have different risks of producing EPS.

Table 1. Comparisons of important parameters of common atypical antipsychotics and binding properties of quetiapine vary depending on the dose.

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Brexpiprazole
Half-life	5-16 hours	20-24 hours	21-54 hours	6-7 hours	6.6 hours	75-146 hours (including active metabolite)	91-177 hours (including active metabolite)
Adminis-tration	Oral	Oral, Depot	Oral acute IM, Depot (not available in Canada)	Oral	Oral, acute IM	Oral, Acute IM, Depot	Oral
Main Mechanism of action	D_2 antagonist, $5HT_{2A}$ antagonist, $5HT_{2C}$, $5HT_{1A}$ antagonist Additionally, clozapine has potent antihistamine, anticholinergic, and α,-adrenergic antagonism action.	D_2 antagonist, $5HT_{2A}$ antagonist, $5HT_7$ antagonist. Additionally, has potent α,-adrenergic antagonism.	D_2 antagonist, $5HT_{2A}$ antagonist, $5HT_{2C}$ antagonist. Additionally, has potent antihistamine and anticholinergic action.	D_2 antagonist, $5HT_{2A}$, $5HT_{2c,}$ $5HT_7$ antagonist, $5HT_{1A}$ partial agonist, norepinephrine reuptake blocker. Additionally, has potent antihistamine, anticholinergic, and α,-adrenergic antagonism action.[a]	D_2 antagonist, $5HT_{2A}$ antagonist, $5HT_{1A}$ partial agonist, $5HT_{2C}$, $5HT_7$, $5HT_{1B/D}$ antagonist	Partial D_2 agonist	Partial D_2 agonist
Primary Indications	Treatment resistant schizophrenia, reduction of suicide risk in those with schizophrenia and schizoaffective disorder	Schizophrenia, other psychotic disorders, acute mania, autism related irritability in children, bipolar maintenance	Schizophrenia, acute agitation in schizophrenia and mania, acute mania, bipolar maintenance, bipolar depression, treatment resistant depression	Acute schizophrenia, schizophrenia maintenance, acute mania, bipolar maintenance, dipolar depression, depression	Schizophrenia, acute agitation in schizophrenia, acute mania, bipolar maintenance	Schizophrenia, acute mania, bipolar maintenance, adjunctive treatment in depression, autism-related irritability in children, Tourette's in children, schizophrenia and bipolar related agitation	Schizophrenia, adjunctive treatment for treatment-resistant depression

Clozapine

In studies, including meta-analyses, comparing Clozapine to first generation antipsychotics, this atypical has been found to produce fewer EPS.[4,13] Research has demonstrated that Clozapine can help significantly reduce tardive dyskinesia in patients already suffering from the disorder, and that it is also less likely to produce this side effect compared to first generation antipsychotics.[7]

However, Clozapine has the rare (0.68%), but potentially life-threatening side effect of agranulocytosis (white blood count <1.0 X 103/mm3), hence requires strict and regular white blood cell count monitoring which can limit its utility.[14, 15]

Risperidone

Risperidone has a higher risk of EPS compared to the other atypical antipsychotics. Specifically, EPS with Risperidone appears to be dose dependent, with symptoms tending to emerge at doses higher than 6 mg.[7] Furthermore, although not common, Risperidone is associated with akathisia and dystonia (<2%), even at low doses.[7,16] However, in one randomized double-blind, placebo-controlled study, Risperidone was found to have a significantly lower incidence of EPS compared to Haloperidol (a commonly prescribed first generation antipsychotic) and consequently required less co-prescribed anti-parkinsonian medication to combat these symptoms.[16] Interestingly, the atypicals have been used to reduce severe EPS caused by previous treatment with first generation antipsychotics.[7] Risperidone, in particular, was found to better reduce iatrogenic parkinsonism, akathisia, and tremor when compared to Haloperidol.[17] However, Risperidone also has side effects including metabolic side syndrome and hyperprolactinemia, which can limit the use of this medication.[18]

Olanzapine

Research has demonstrated that Olanzapine has a lower incidence of EPS compared to the first generation antipsychotics.[5] One paper that examined three randomized, double-blind studies found that Olanzapine resulted in significantly fewer EPS (dystonais, parkinsonism, and akathisia) compared to Haloperidol.[19] Furthermore, a blind, controlled, study found that the appearance of tardive dyskinesia was significantly lower in those taking Olanzapine as compared to typical antipsychotics.[20] However, it is important to note that 2.5%-18% of patients, depending on how EPS is defined, still experienced some form of EPS while on Olanzapine. Although this is significantly lower than the 33.3-46.5% seen with the typical antipsychotic medications, EPS are clearly still a major complication that must be monitored for in those receiving Olanzapine.[18,21]

Quetiapine

In a double blind, randomized study comparing Quetiapine to Haloperidol, this atypical had significantly lower rates of EPS. Fewer patients required pharmacological treatment for EPS while on Quetiapine, and no participants withdrew due to EPS.[22] Furthermore, studies have found that, on low to high doses (250mg-750mg), EPS rates were comparable to those observed in patients in the placebo (no medication) group.[23]

Ziprasidone

Some patients have found that while on Ziprasidone, they experience either no change, or fewer EPS after four weeks of administration, and rates of EPS are lower when compared to first generation antipsychotics.[24] Furthermore, a double-blind, placebo-controlled study, found that Ziprasidone performed better than placebo in reducing akathisia ratings after one year of drug administration.[25]

Aripiprazole

Aripiprazole is one of the more recently available atypical antipsychotics.[4] In a study comparing Aripiprazole, Haloperidol, and placebo in hospitalized patients, participants experienced fewer EPS on Aripiprazole compared to Haloperidol, with rates similar to those seen in the placebo group.[26] Furthermore, patients were much more likely to discontinue using Haloperidol than Aripiprazole due to EPS (rates of discontinuation being 3% versus 0.8%, respectively). However, it is important to mention that while akathisia ratings were lower in the Aripiprazole group compared to the Haloperidol group, akathisia rates in this atypical were significantly higher than placebo when all doses ranges were considered.[26] This adverse effect can limit its clinical utility.

Brexpiprazole

Brexpiprazole is a relatively new atypical antipsychotic that is marketed as having few adverse effects. Much like Aripiprazole, Brexpiprazole has low levels of EPS at clinical doses. In fact, one study found that incidences of akathisia were lower in the Brexpiprazole group than in the placebo group, and proposed it as a better alternative to Aripiprazole.[27] However, another study found akathisia to be more common in those taking the medication compared to placebo.[27] While there was a higher risk of EPS in those taking 4mg/day compared to 2mg/day, overall the risk of EPS with Brexpiprazole appears to be low.[27,28]

Mechanisms of extrapyramidal symptoms reduction

The various atypical antipsychotics act differently on the brain's neuroreceptors, and there is debate as to why some of these medications have lower incidence of EPS than others, and when compared to the first generation antipsychotics. Some studies have suggested that atypical antipsychotics have a higher antagonistic affinity for the 5-HT2 serotonin receptors than they do for the D2 dopamine receptors.[2] Generally, it is believed that EPS are caused by dopamine antagonism in the striatum. Some hypothesize that the serotonin antagonism of the atypicals may help to alleviate EPS by lessening dopamine inhibition in the striatum.[29] Specifically, it is thought that serotonin antagonists act as part of a feedback loop in the basal ganglia, increasing

dopamine release, and that this release eases EPS; however, some evidence exists which challenges this claim.[5] For instance, some of the first generation antipsychotics also have high serotonin antagonism, yet still produce a high degree of EPS.[2] Another more widely supported, hypothesis proposed to describe the mechanism of reduced EPS associated with atypical antipsychotics is that atypicals have a more rapid dissociation from the D2 dopamine receptor as compared to the first generation antipsychotic agents.[30] This is supported by evidence that EPS seems to occur only once D2 occupancy exceeds 80%.5 Despite preliminary support for the D2 dissociation hypothesis, several questions remain, and further research is required to confirm this mechanism. For instance, if over 80% D2 occupancy is the sole cause of EPS, and a lack of such occupancy the sole cause of EPS reduction, then one would expect no EPS with the atypical antipsychotics, so long as these did not exceed 80% D2 occupancy. However, as previously stated, this is not the case, as EPS still do occur with the atypicals. Furthermore, it does not explain why some EPS occurs years after initiation of the medication.

It is important to have a more complete understanding of the mechanism that underlies the EPS reduction associated with atypical antipsychotics, as this may facilitate the development of targeted treatment to better reduce EPS. In addition, understanding the mechanism behind EPS can help us to better understand potential drug interactions that could exacerbate EPS. Thus, it is essential that more research be conducted towards the elucidation of the mechanisms of EPS and its reduction so that these clinical issues can be addressed.

Special considerations for extrapyramidal symptoms

An important consideration in the administration of atypical antipsychotics is determining which patients are most vulnerable to developing EPS. Despite the fact that this information would be very useful to physicians prescribing such medications, there is relatively little research on the topic. One systematic review that is available on EPS vulnerability found that bipolar patients in a depressive state are at a higher risk of EPS compared to schizophrenic patients, with rates varying depending on the antipsychotic used.[31] Other studies suggest that older patients are at greater risk of parkinsonism effects, perhaps due to an age-related reduction in striatal dopamine, whereas younger patients are at greater risk of developing acute dystonia due to a stronger dopamine response.[5] Recently, one study found that schizophrenic patients who are placed on adjunctive Carbamazepine along with an atypical are also at greater risk for EPS development.[32] This has important implications, since vulnerability to EPS may affect the dose that physicians can safely prescribe before EPS becomes a serious side effect. Preventing these side effects is of particular concern because EPS, and akathisia in particular, results in lower antipsychotic compliance. In fact, there is suggestion that akathisia results in increased suicidality.[12]

There are also several factors which may prevent EPS reduction. First, due to the nature of the disorders that require treatment with antipsychotics, there may be certain cognitive issues that prevent physicians from successfully diagnosing drug induced EPS.[5] For instance, a catatonic patient may be unable to communicate with their healthcare team about their EPS.

Furthermore, it may be difficult for physicians to differentiate between EPS and symptoms of schizophrenia, such as responding to auditory, visual, tactile, and gustatory hallucinations, as well as waxy flexibility.[5] For example, a patient who appears to be muttering to themselves in response to an auditory hallucination, may actually have an oral dyskinesia. Given the unpleasant and potentially serious nature of EPS, it is essential that there exist effective measures of their presence and severity, especially for those patients where diagnosis may be more difficult. Therefore, it is paramount to administer some form of EPS screening. One commonly used approach is the administration of the Abnormal Involuntary Movement Scale (AIMS) at baseline and then regularly after the prescription of atypical antipsychotics to check for the emergence of EPS, especially tardive dyskinesia.[33] This monitoring should allow physicians to make necessary medication adjustments (i.e. changing medications, adding combative medications, or decreasing dosage) to reduce EPS if they occur, and consequently promote patient compliance.

Reducing extrapyramidal symptoms

Given the potentially serious and often unpleasant nature of EPS, it is essential that physicians are educated about methods of reducing these symptoms. Historically, with the first generation antipsychotics, physicians relied on polypharmacy to manage EPS. β-blockers and benzodiazepines continue to remain potential treatment options for those suffering from drug-induced akathisia, although they have limited efficacy.[34] Anticholinergics are another potential option used to offset EPS. Specifically, they can be effective as a short-term prophylactic agents, and have been shown to be particularly effective for the treatment of acute dystonia. However, these medications can cause significant unpleasant side effects, including dry mouth, blurred vision, and confusion.[35] Furthermore, polypharmacy poses several problems in itself. For instance, it increases the risk of other potentially negative side effects, and increases the difficulty in managing these effects. Polypharmacy requires continual monitoring by a physician and careful consideration of the various drug interactions.[36] It is for these reasons that atypical antipsychotics may be a better choice than first generation medications. This is reflected in practice guidelines, which advise lowering dosages, rather than adding medications, as a first response for dealing with atypical antipsychotic-induced EPS.[4]

Atypical antipsychotics and metabolic syndrome

Although atypical antipsychotics are thought to be associated with lower degrees of EPS, other serious side effects that can accompany these medications include Metabolic Syndrome.[37] Metabolic Syndrome is a cluster of conditions, including Obesity, insulin insensitivity, Hypertension, Dyslipidemia (cholesterol and triglyceride abnormalities), and low levels of high density lipoproteins, that often lead to other serious consequences, such as Cardiovascular Disease and Diabetes.[37,38]

Weight gain due to use of atypical antipsychotics is a common and often prohibitive side effect due to its negative effect on patient health and compliance with the medication. This side effect purportedly occurs due to the antagonism of hypothalamic histamine (H1) and serotonin (5HT2c) receptors resulting in increased appetite. Furthermore, although the mechanism is currently unknown, it is thought that second-generation antipsychotics also alter glucose metabolism by increasing insulin resistance.[37] Clozapine, in particular, is associated with a significant amount of weight gain, as well an increased risk of developing Type 2 Diabetes Mellitus.[7] Furthermore, a post hoc analysis of the observational Worldwide Schizophrenia Outpatient Health Outcomes database found that while weight gain is most significant during the first six months of treatment, it persists even years later while continuing to take the medication.[39] Some studies have examined whether these symptoms can be reduced via pharmacological treatments, and indeed, there have been some promising results.[37] For instance, a meta-analysis found that metformin is effective in the reduction of weight gain and insulin resistance.[40] Unfortunately, these positive effects seem to dissipate with cessation of this medication. [41] Recently, studies have also looked at the use of Liraglutide for the treatment of Metabolic Syndrome in those with Schizophrenia taking Clozapine and Olanzapine. It was found that Liraglutide significantly improved glucose tolerance and glycemic control, and also resulted in weight loss.[42] Unfortunately, the need for additional medications in order to combat side effects once again necessitates confrontation of the potential issues associated with polypharmacy. The nature of metabolic syndrome and the treatment it requires puts into question whether the benefits of atypicals (i.e., reduction in EPS liability) outweigh the risks associated with metabolic syndrome. That being said, research has looked into non-pharmacological methods of reducing the risk of metabolic syndrome. Aerobic interval training and strength training has been shown to have promising results towards this end.[43] Other studies have shown that placing patients on weight-management programs significantly helps with weight loss, and prevention of further weight gain in patients on atypical antipsychotics. Notably, the effectiveness of various therapeutic interventions depends on the characteristics of the patient. For instance, those with chronic Schizophrenia respond better to recreation-type interventions, with the added benefit that these also aid in future social interaction. On the other hand, younger individuals with recent-onset psychosis tend to respond more favourably to more flexible, individualized therapies that involve diet, exercise, and behavioural modifications.[44]

Unfortunately, many of the studies looking at Metabolic Syndrome in those taking atypical antipsychotics focus on weight loss after Metabolic Syndrome has already taken effect. There are considerable gaps in the literature regarding effective preventative methods. However, one study found that weight gain was significantly reduced in patients that underwent a nutrition management program (promoting diet, exercise, and healthy food intake) in those starting Olanzapine.[45] Given these promising results, it seems that Metabolic Syndrome can be prevented in some patients through non-pharmacological therapeutic interventions. However, it is clear that further research needs to be conducted on the prevention of Metabolic Syndrome on those taking atypicals. Specifically, different non-pharmacological treatments should be considered, and the

effectiveness of various treatments should be tested with for each atypical and with different populations (e.g., chronic vs. recent-onset psychosis, young vs. older patients, patients of different ethnicities, etc.). Once this information is available, physicians will be better able to understand the metabolic consequences of prescribing atypical antipsychotics, and will be better equipped to help patients avoid the serious risks associated with metabolic syndrome. If future studies suggest that Metabolic Syndrome can be effectively prevented via non-pharmacological therapies, then the risk-benefit ratio would likely favour the atypical antipsychotics as compared to the first generation antipsychotics. This would go a long way toward increasing physician comfort and confidence in prescribing atypicals to their patients.

Future directions

Overall, it appears that the atypical antipsychotics are a superior treatment for psychosis as compared to the first generation antipsychotics. This is especially true with regard to the recent atypicals that are emerging on the market, some of which are favourable with respect not only to EPS, but also with respect weight gain and metabolic effects. The atypicals as a class, have lower EPS liability, and studies support that Metabolic Syndrome associated with treatment with atypical antipsychotics can be at least somewhat controlled with interventions involving diet and exercise.[44] That being said, more research needs to be conducted on the various atypical antipsychotics and how they affect patient quality of life. Specifically, it is important that we develop a greater understanding of the impact in this regard of both EPS and metabolic syndrome on these patients. Future research should delve into the demographics (e.g., age, sex, ethnicity, type of disorder, occupation, etc.) of individuals being treated with antipsychotics, and attempt to determine the risk-benefit profile for each group. Although it is important to carefully monitor for both of these side effects, and ideally, we would prefer that patients experience neither, it is possible that a specific patient population may be more susceptible to developing one side effect over another. In other words, certain groups might report a lower negative impact upon quality of life with EPS. For example, someone who is already significantly overweight with a positive family history of diabetes may be less impacted by the metabolic side effects of atypical antipsychotics than someone whose livelihood involves excellent fine motor control may be effected by EPS. This information is important, as it could help to inform value-sensitive prescribing. Specifically, it would assist clinicians in determining which antipsychotic should be prescribed to each individual patient based on the least detrimental side effect profile for that individual.

Another important consideration in the prescription of atypical antipsychotics is drug interactions. Although extensive research has been conducted on how various drugs react with the atypical antipsychotics, specifically with regard to research involving enzyme metabolism, relatively little work has been done to investigate how drug interactions affect EPS.[46] Further research should be conducted in this area to help prevent EPS in patients taking atypical

antipsychotics together with other medications, including for augmentation, as well as for comorbid psychiatric and medical conditions.

Conclusion

The current available literature suggests that the atypical antipsychotics appear to be a better alternative than the first generation antipsychotics. While this really is a matter of finding the treatment with the least detrimental side effects (i.e. EPS vs. Metabolic Syndrome) on a case-by-case basis, overall the atypicals have lower EPS risk. Furthermore, Metabolic Syndrome, while certainly serious, can be more effectively treated, and perhaps even prevented, with non-pharmacological interventions. The research suggests that pharmacological agents, while not ideal in either case, seem to be more effective in combating Metabolic Syndrome than EPS. However, it is still vitally important that physicians are aware of the risks associated with the atypical antipsychotics, including EPS, and that patients on these medications are extensively and regularly monitored for the associated side effects. Finally, it is clear that more research needs to be conducted on the atypical antipsychotics and the significant side effects associated with them. Particular attention should be paid to understanding the mechanisms of both EPS and Metabolic Syndrome, and the impact these side effects have upon patients' quality of life.

Acknowledgements

I would like to acknowledge Dr. Marion Perpick-Breton for editing this manuscript.

References

1. Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomised trials. BMC Psychiatry. 2007; 7(1): 40.
2. Kapur S, Remington G. Atypical antipsychotics: new directions and new challenges in the treatment of schizophrenia. Annual Reviews in Medicine. 2001; 52: 503-517.
3. Shen WW. A history of antipsychotic drug development. Comprehensive Psychiatry. 1999; 40(6): 407-414.
4. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: Incidence, prevention and management. Drug Safety. 2005; 28(3): 191-208.
5. Weiden P. EPS profiles: the atypical antipsychotics are not all the same. Journal of Psychiatric Practice. 2007; 13(1): 13-24.
6. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs. 2002; 16(1): 23-45.
7. Kaplan HI, Sadock BJ. (eds). Comprehensive textbook of psychiatry 9th ed., Vols. 1-2. Philadelphia, PA: Williams & Wilkins Co. 2009.

8. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics. Part 1: pharmacology, pharmacokinetics, and efficacy. Annals of Pharmacotherapy. 1999; 33(1): 73-85.
9. Stahl SM. (eds). Stahl's essential psychopharmacology prescriber's guide sixth edition. New York, NY: Cambridge University Press. 2017.
10. Lam RW, McIntosh D, Wang J, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 1. disease burden and principles of care. The Canadian Journal of Psychiatry. 2016; 61(9): 510-523.
11. Bürki HR. Extrapyramidal side-effects. Pharmacology & Therapeutics 1979; 5: 525-534.
12. Tandon R, Jobson MD. Extrapyramidal side effects of antipsychotic treatment: scope of problem and impact on outcome. Annals of Clinical Psychiatry. 2002; 14(2): 123-129.
13. Wahlbeck K, Cheine M, Essali A, et al. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. American Journal of Psychiatry. 1999; 156(7): 990-999.
14. Ingimarsson O, MacCabe JH, Haraldsson M, et al. Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. BMC Psychiatry. 2016; 16: 441.
15. Schulte, PF. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. Annals of Pharmacotherapy. 2006; 40: 683-8.
16. Simpson GM, Lindenmayer JP. Extrapyramidal symptoms in patients treated with risperidone. Journal of Clinical Psychopharmacology. 1997; 17(3): 194-201.
17. Heck AH, Haffmans PMJ, De Groot IW, et al. Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double-blind, multi-center trial. Schizophrenia Research. 2000; 46(2): 97-105.
18. Chen JX, Su YA, Bian QT, et al. Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: a randomized, double-blind, placebo-controlled, dose-response study. Psychoneuroendocrinology. 2015; 58: 130-140.
19. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. The Journal of Clinical Psychiatry.1997; 58(6): 205-211.
20. Tollefson GD, Beasley CM, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. American Journal of Psychiatry.1997; 154(9): 1248-1254.
21. Buoli M, Kahn RS, Serati M, et al. Haloperidol versus second generation antipsychotics in the long term treatment of schizophrenia. Human Psychopharmacology: Clinical & Experimental. 2016; 34(4): 325-331.
22. Arvaniti LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biological Psychiatry.1997; 42(4): 233-246.

23. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high-and low-dose double-blind comparison with placebo. Archives of General Psychiatry.1997; 54(6): 549-557.
24. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. Journal of Clinical Psychopharmacology.1998; 18(4): 296-304.
25. Arato M, O'Connor R, Meltzer HY, et al. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the ziprasidone extended use in schizophrenia study. International Clinical psychopharmacology.2002; 17(5): 207-215.
26. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: Safety and tolerability in short-term, placebo-controlled trials. Schizophrenia Research.2003; 61: 123-136.
27. Das S, Barnwal P, Winston AB, et al. Brexpiprazole: so far so good. Therapeutic Advances in Psychopharmacology.2016; 6(1): 39-54.
28. Kishi T, Oya K, Matsui Y, et al. Comparison of the efficacy and safety of 4 and 2 mg/day brexpiprazole for acute schizophrenia: a meta-analysis of double-blind, randomized placebo-controlled trials. Neuropsychiatric Disease and Treatment.2018; 14: 2519-2530.
29. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. American Journal of Psychiatry.1996; 153(4): 466-476.
30. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? a new hypothesis. The American Journal of Psychiatry.2001; 158(3): 360-369.
31. Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. Journal of Clinical Psychopharmacology.2008; 28(2): 203.
32. Ribeiro SB, De Arauji AA, Medeiros CA, et al. Factors associated with expression of extrapyramidal symptoms in users of atypical antipsychotics. European Journal of Clinical Pharmacology.2017; 73(3): 351-355.
33. Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. Hospital Community Psychiatry.1988; 39(11): 1172-1177
34. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Safety.2000; 22(1): 73-81.
35. Ogino S, Miyamoto S, Miyake N, et al. Benefits and limits of anticholinergic use of schizophrenia: focusing on its effect on cognitive function. Psychiatry and Clinical Neurosciences.2013; 68(1): 37-49.
36. Advokat CD, Comaty JE, Julien RM. (eds). Julien’s primer of drug action: a comprehensive guide to the actions, uses, and side effects of psychoactive drugs 13th ed. New York: Worth Publishers.2014.

37. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. Current Opinion in Endocrinology, Diabetes, and Obesity.2010; 17(5): 460-466.
38. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome: a new worldwide definition. The Lancet.2005; 366: 1059-1062.
39. Bushe CJ, Slooff CJ, Haddad, et al. Weight change from 3-year observation data: Findings from the worldwide schizophrenia outpatient health outcomes database. Journal of Clinical Psychiatry.2012; 73(6): 749-755.
40. De Silva VA, Suraweera C, Ratnatunga SS, et al. Metformin in prevention and treatment of antipsychotic induced weight gain. a systematic review and meta analysis. BMC Psychiatry.2016; 16: 341.
41. Rojo LE, Gaspar PA, Silva H, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: a global challenge for modern psychopharmacology. Pharmacological Research.2015; 101: 74-85.
42. Larsen JR, Vedtofte L, Jakobsen MSL et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine or olanzapine treated patients with schizophrenia spectrum disorder. JAMA Psychiatry.2017; 74(7): 719-728.
43. Stensvold D. Strength training versus aerobic interval training to modify risk factors of metabolic syndrome. Journal of Applied Physiology.2010; 108(4): 804-810.
44. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, et al. Non-pharmacological management of antipsychotic-induced weight gain: a systematic review and meta-analysis of randomised controlled trials. The British Journal of Psychiatry.2008; 193(2): 101-107.
45. Evans S, Newton R, Higgins S. Nutritional intervention to prevent weight gain in patients commenced on olanzapine: A randomized controlled trial. Australian and New Zealand Journal of Psychiatry.2005; 39(6): 479-486.
46. Urichuk L, Prior TI, Dursun S, et al. Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. Current Drug Metabolism.2008; 9(5): 410-418.

Commentary

Is there a limit to human life expectancy?

Alexander Levesque

Western University Schulich School of Medicine & Dentistry, London, Canada

Abstract

The analysis and prediction of life expectancy trends hold an important role in many aspects of our society. On a macro level, governments rely on life expectancy data to make decisions about public welfare programs, health care, retirement age, and pension programs. On an individual level, many people take life expectancy data into account when planning their retirements and making decisions about their future. Currently, two main schools of thought dominate the debate on the trajectory of life expectancy trends. The Olshansky School argues that global human life expectancy is reaching its absolute limit and predicts that a worldwide plateau in life expectancy will soon be reached. The Vaupel School, however, believes that such a plateau is nowhere in sight, and that humans possess no biological barrier that will prevent life expectancy from increasing indefinitely. In this commentary, I build upon the evidence generated by the Vaupel School by introducing socioeconomic factors into the debate and I argue that with consistent improvements to medical technology and general prosperity we will not encounter a biological limit to human life expectancy in our lifetimes.

Keywords: life expectancy; life span; longevity; mortality

Corresponding author: alevesque2022@meds.uwo.ca

Introduction

Life expectancy trends have a critical impact on government decisions about public welfare programs, health care, retirement age, and pension programs.[1,2] Many individuals also rely on life expectancy data when planning their retirements and making decisions about their future.[1] Therefore, it is no surprise that so many people are interested in the question, "Is there a natural limit to human life expectancy?" The goal of this commentary is to present evidence addressing this question and to argue that a limit to human life expectancy is nowhere in sight. Two opposing ideologies dominate the discussion on life expectancy limits: the "Olshansky School" and the "Vaupel School".[3] In the first section I will present the ideas of the Olshansky School, which adamantly insists that global human life expectancy is approaching its absolute limit, in order to establish the arguments I hope to refute in this paper. In the next two sections I will present the demographic and biologic arguments of Vaupel and his supporters, who use life expectancy trends to demonstrate an optimistic outlook for human mortality. In the final section, I extend the position of the Vaupel School by introducing a socioeconomic side to the argument, which I believe addresses one of the main criticisms of the Vaupel School. In sum, my arguments will demonstrate there is little reason to assume we will hit a life expectancy limit in our lifetimes.

The Olshansky School

The central argument of the Olshansky School is that as expectations of life expectancy at birth increase, life expectancy becomes less sensitive to changes in death rates, meaning it will inevitably plateau.[3] This argument is rooted in two interrelated principles. The first is Fries Theory, also called the limited life-span theory, which predicts that human life expectancy is capped at around 85 years of age due to internal, physiological processes—namely the reduction in organ capacity and compensation that inevitably occurs with age.[3,4] The second important concept to the Olshansky School is the theory of entropy. As applied to life tables, the entropy phenomenon causes the magnitude of the reductions in age specific mortality rates (ASMR) necessary to improve life expectancy to grow substantially as life expectancy increases.[2] This means that gains in life expectancy should naturally slow down over time as the reduction in mortality rates needed to sustain these gains increases exponentially, requiring an almost endless stream of medical innovation.[2] It is these two theories that shape the majority of the Olshansky School's work.

In 2001, Olshansky, Carnes, and Désesquelles published a paper intended to support and correct predictions made in the Olshansky School's original 1990 paper.[2] In their revised paper, which focuses on life expectancy trends in France, Japan, and the United States (US), the authors concluded that a life expectancy of 100 is extremely unlikely, while the idea of a life expectancy ever surpassing 100 is impossible.[2] As evidence, they demonstrated that reaching a life expectancy of 100 in Japan or France requires an 85% reduction in ASMR at all ages.[2] In

addition, due to the entropy phenomenon, if the same magnitude of mortality reductions that occurred between 1900 and 1995 in the U.S., which increased life expectancy by thirty years, occurred in 1995 it would only result in a 10.1 year increase in life expectancy.[2] Finally, the authors pointed out that the ASMR decreases seen in the 20th century were due to dramatic reductions in infant mortality and deaths from infectious diseases, reductions that are unlikely to be repeated.[2]

From this paper, and similar evidence presented in more recent papers, the Olshansky School concludes that the limited life-span theory is essentially correct, although the limit may be higher than 85 years.[5,6] The reductions in ASMR needed for further increases in life expectancy are significantly greater now, while developing the necessary medical interventions will be objectively harder than preventing infectious diseases or infant mortality.[2,5] The Olshansky School also draws attention to new life expectancy threats; namely obesity, antibiotic resistance, and global pandemics.[3] There is also evidence that, unlike life expectancy, the maximum age that any human has lived to (a number that is much less influenced by environment and lifestyle) is not increasing substantially.[7] This suggests an ultimate life expectancy cap that sits at around 115 years, barring a radical change in the aging process of humans.[7] Overall, the Olshansky School emphasizes underlying biological mechanisms and empirical evidence that it believes demonstrates life expectancy is reaching its limit.

A demographic rebuttal

The Vaupel School's major rebuttal to the arguments of the Olshansky School hinges on Vaupel's analysis of trends for the record-holding female life expectancy over time. Through analyzing these trends, the Vaupel School discovered that the record-holding female life expectancy has increased linearly (r^2 of 0.992) by three months every year for the past 160 years.[1] In other words, while gains in individual countries' female life expectancy may appear to be slowing, the record for the highest female life expectancy consistently grows every year with shocking linearity. Oeppen and Vaupel point out that if life expectancy was reaching a limit then this trend should be decelerating, but more recent evidence suggests that it is not.[1,3] The Vaupel School believes their finding illustrates that life expectancy increases are due to continuous innovation, refuting the Olshansky School's claim that the gains experienced from reducing infectious disease and infant mortality are unrepeatable today.[3] The Vaupel School also launches valid criticisms against proponents of the limited life-span theory, pointing out that they are consistently wrong in their predictions. For example, the limits set by the Olshansky School in 1990 were surpassed in only five years, and several of their 2001 predictions were also surpassed soon after they were made.[3]

The Vaupel School's own predictions for life expectancy are much more optimistic. They expect that current trends should continue relatively undisturbed into the future, meaning global life expectancy should rise nearly linearly and break 85 years by 2050.[3] Vaupel and his collaborators are also not alone in their optimism, as a recent survey of demographic experts

suggests most agree with the Vaupel School's optimistic outlook.[3] Kontis et al. (2017) further support this optimistic perspective in their recent paper, which uses 21 models and life table analysis to probabilistically predict future life expectancy increases.[8] They found that there is a greater than 50% chance that life expectancy in South Korea will break the 90-year threshold by 2030.[8] There is also a 65% chance and an 85% chance that women and men, respectively, see a life expectancy increase by 2030 in all 35 industrialized countries studied by Kontis et al.[8] These findings alone question the idea that life expectancy gains are decelerating. However, Kontis et al. also found that a majority of the predicted gains in female life expectancy are due to decreased ASMR above age 65, further refuting the Olshansky School's insistence that reducing ASMR at older ages is too challenging.[8] Altogether, these findings illustrate that Vaupel is not alone in doubting the claims of the Olshansky School.

A biological rebuttal

The Vaupel School has also provided sufficient evidence to dispute the limited life-span theory and the biological arguments of the Olshansky School. For one, several studies have demonstrated that ASMR actually decelerates with increasing age, starting at around age 80.[9] Furthermore, the risk of dying plateaus at around 50% starting at 103 and 107 years of age for men and women respectively.[10] Therefore, contrary to the theories of the Olshansky School, there appears to be no age in humans where a biological barrier causes rapid acceleration of ASMR. Additionally, while mortality rates may decelerate and plateau at older ages, rates of deterioration are not decelerating.[11] Instead, demographic trends suggest physical deterioration is being postponed to later and later ages while the duration of senescence remains the same, meaning medical interventions are not simply increasing the duration of time one can live past a preset physiological barrier.[11] Finally, a study of Danish identical twins revealed that twins do not share a genetically predetermined maximum life span, as only about 25% of the variation in life expectancy was attributable to genetics, casting further doubt on the limited life span theory.[12,13] Overall, the Vaupel School has demonstrated sufficient evidence from human studies to at least question the validity of the Olshansky School's arguments.

Through their major demographic and biological arguments, the Vaupel School manages to refute most of the arguments of the Olshansky School. However, Vaupel and his collaborators fail to directly address evidence that the maximum age at death continues to sit around 115 years, regardless of plateaus in ASMR. Instead, the Vaupel School proposes that consistent increases in life expectancy occur through consistent innovations in medical technology and improvements to general prosperity.[11] Essentially, as people reach old age in better health and with access to improved health technology, they are able to live longer and delay senescence further.[11] This perspective implies that the current maximum age at death will eventually be surpassed, given time. The Vaupel School also does not directly address the Olshansky School's criticism of optimum lifestyle predictions as ignoring biological influences. In other words, the Olshansky

School posits that by focusing on the best performing countries and individuals, and suggesting individual lifestyles are the most important determinant of survival, the Vaupel School emphasizes outlying over-performers while ignoring the biological processes that are decelerating life expectancy trends in most populations.[3] I would propose, however, that it is growing socioeconomic inequality and not biological processes responsible for the decelerating life expectancy trends observed in many populations, and, by focusing on best-practice life expectancy, the Vaupel School is demonstrating the trajectories that are possible without the influences of socioeconomic inequality.

A socioeconomic rebuttal

The socioeconomic determinants of life expectancy have an established space in the debate over life expectancy trends, namely in the discussion of so called "best practice" life expectancy, which tries to account for mortality risk factors.[1,2] Throughout the world, growing socioeconomic inequality mirrors stagnation and declines in life expectancy trends.[14,15] Cross-national analysis of Gini coefficients (a measure of inequality) reveals that higher national economic inequality is significantly associated with a lower national life expectancy.[1] Furthermore, changes in inequality over time are significantly associated with changes in life expectancy.[1] Taken together, this international data suggests that growing inequality is masking what would otherwise be significant gains in life expectancy in many countries. In the US, for example, the gap in life expectancy between the richest 1% and the poorest 1% is 14.6 and 10.1 years for men and women respectively, and this gap is growing over time.[11] This means that the top 1% of the US continues to achieve substantial gains in life expectancy over time, even while the life expectancy of the rest of the country plateaus. While the Olshansky School may reject the Vaupel School's optimum lifestyle predictions and risk factor approaches for ignoring biological influences, these approaches can reveal the true gains in life expectancy that may be hidden by socioeconomic inequality.

Conclusion

The Vaupel School's demographic and biological arguments refute the majority of the claims made by the Olshansky school and demonstrate that the Olshansky School is wrong to conclude that life expectancy gains are decelerating or reaching their limit. The one major criticism that the Vaupel School does not address—the weaknesses of relying on best-practice and risk-factor analyses—is accounted for in my examination of the influence of growing socioeconomic inequality on life expectancy trends. Overall, the overwhelming majority of the evidence presented in this paper rests firmly against the arguments of the Olshansky School. This does not mean that no life expectancy limit exists conclusively, as there are many biological, physical, and chemical processes about which we understand little. Instead the evidence presented here

strongly indicates that none of us will encounter a life expectancy limit during our lifetime. Good news for those of us who wish to see humans reach immortality, but perhaps alarming for those who have neglected to plan for their retirements.

References

1. Oeppen J, Vaupel JW. Broken limits to life expectancy. Science. 2002 May 10;296(5570):1029.
2. Olshansky SJ, Carnes BA, Désesquelles A. Prospects for human longevity. Science. 2001 Feb 23;291(5508):1491-2.
3. Caselli G, Drefahl S, Wegner-Siegmundt C, Luy M. Future mortality in low mortality countries. In: Lutz W, Butz WP, KC S, editors. World Population & Human Capital in the Twenty-First Century: An Overview. Oxford: University Press; 2017.
4. Fries JF. Aging, natural death, and the compression of morbidity. N Engl J Med. 1980 Jul;303(3):130-5.
5. Olshansky SJ, Carnes BA. Zeno's paradox of immortality. Gerontology. 2013;59(1):85-92.
6. Carnes BA, Olshansky SJ, Hayflick L. Can human biology allow most of us to become centenarians?. J Gerontol A Biol Sci Med Sci. 2012 Aug 9;68(2):136-42.
7. Vijg J, Le Bourg E. Aging and the inevitable limit to human life span. Gerontology. 2017;63(5):432-4.
8. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017 Apr 1;389(10076):1323-35.
9. Vaupel JW, Carey JR, Christensen K, Johnson TE, Yashin AI, Holm NV, et al. Biodemographic trajectories of longevity. Science. 1998 May 8;280(5365):855-60.
10. Modig K, Andersson T, Vaupel J, Rau R, Ahlbom A. How long do centenarians survive? Life expectancy and maximum lifespan. J Intern Med. 2017 Aug;282(2):156-63.
11. Vaupel JW. Biodemography of human ageing. Nature. 2010 Mar 24;464(7288):536.
12. McGue M, Vaupel JW, Holm N, Harvald B. Longevity is moderately heritable in a sample of Danish twins born 1870–1880. J Gerontol. 1993 Nov 1;48(6):B237-44.
13. Herskind AM, McGue M, Iachine IA, Holm N, Sørensen TI, Harvald B, et al. Untangling genetic influences on smoking, body mass index and longevity: a multivariate study of 2464 Danish twins followed for 28 years. Hum Genet. 1996 Aug 1;98(4):467-75.
14. Babones SJ. Income inequality and population health: correlation and causality. Soc Sci Med. 2008 Apr 1;66(7):1614-26.
15. Chetty R, Stepner M, Abraham S, Lin S, Scuderi B, Turner N, et al. The association between income and life expectancy in the United States, 2001-2014. JAMA. 2016 Apr 26;315(16):1750-66.

Commentary

Novel evidence depicting adverse long-term outcomes linked to tonsillectomy: a spotlight on overtreatment

Nikhil Nair Hariharan[a] and Kashyap Patel[b]

[a]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Canada

[b]Faculty of Health Sciences, McMaster University, Hamilton, Canada

Abstract

Tonsillectomies (TEs) are the first line of treatment when patients present with recurrent tonsillitis, peritonsillar abscesses or obstructive sleep apnea. Though TEs have modest efficacy, they remain a common pediatric surgery in Canada. TEs are now viewed as a prophylactic measure used to prevent tonsil-related diseases. Simultaneously, there is a lack of evidence-based decision-making when recommending TEs, leading to overtreatment. Novel findings indicate that pediatric TE patients have an increased risk of complications and poor long-term outcomes including respiratory, infectious, and allergic disorders. A need for alternatives to TEs is evident; less invasive interventions with fewer perioperative complications and lifelong morbidities warrant further research. To prevent unnecessary adverse outcomes, healthcare providers should opt for more selective and evidence-based TE recommendations. Meanwhile, it is also imperative that physicians clearly communicate the potential quality of life implications associated with TEs. Healthcare and social mores surrounding TEs need to change towards a more evidence-based practice that focuses on improving patients' quality of life. This commentary examines the current role of TEs, their long-term outcomes, and the implications of overtreatment.

Keywords: pediatric, tonsillectomy, tonsil-related diseases, tonsil-related surgery, evidence-based, overtreatment

Corresponding author: hariharn@mcmaster.ca

Introduction

A tonsillectomy (TE) is the surgical removal of tonsils and is commonly performed in children. This procedure involves the dissection of the peritonsillar space and ligation of the relevant blood vessels to maintain hemostasis. This surgery is often accompanied with an adenoidectomy (AE), the removal of adenoids, and is mainly performed in patients presenting with recurrent tonsillitis, peritonsillar abscesses or obstructive sleep apnea[1].

TEs have become exceedingly prevalent in contemporary practice. Data reporting in Canada found 3606 children from the age of 0 to 4 years underwent TEs in 2016-2017, making it the most common surgical procedure in that age group. This continues to be a problem in children aged 5 to 17 years, where 3714 individuals underwent TEs during the same period[2]. According to a Cochrane Review on the efficacy of TEs for treating tonsillitis, the benefits conferred by patients were small. It indicated a minor reduction in sore throat episodes when compared to non-surgical treatment[3]. This implies that a large cohort of patients undergo TEs despite their modest benefits[4].

A UK cohort study followed 15,760 children aged 0 to 15 years who underwent TEs from 2005 to 2016 and evaluated the incidence of evidence-based indications for TEs[5]. Evidence-based indications for TEs according to the Paradise criteria include tonsillar tumours, symptoms fitting the Paradise criteria as well as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome (see Table 1)[5]. The study found that the proportion of non-evidence-based TEs was much higher than evidence-based TEs, with "seven in eight children unlikely to benefit"[5]. Instead of being recommended using the Paradise Criteria, TEs are now viewed as a prophylactic measure that serve to prevent any tonsil-related diseases[6-8]. Thus, TEs are not always performed through an evidence-based approach.

Next, the frequency of perioperative complications and morbidities are discussed. Postoperative hemorrhage is a potentially life-threatening major complication incurred by 0.1% to 4.8% of all pediatric patients[9]. TEs can be achieved through cold dissection, which involves "cold" surgical instruments, or through electrosurgery which entails bipolar diathermy. Multiple studies demonstrate higher risks of postoperative secondary hemorrhage after electrosurgery for TE when compared to cold dissections[5,10-12]. According to a nationwide study done in the United States, nearly 3.6% of children are readmitted to hospitals following TEs primarily due to hemorrhages (26%), post-TE pain (16%) and dehydration (47%)[13]. Furthermore, a Thai study indicated that 48% of TE patients reported wound pain and 29% reported dysphagia[14]. Another minor TE complication includes postoperative taste disturbance; 8.6% of patients in a study evaluating this outcome experienced this and it usually lasted for 1.5 months[15]. TEs present a risk of major complications and adverse outcomes including postoperative hemorrhage, readmission to hospital, and temporary changes of sensation on the tongue. Patients and their surgeons should consider this procedure carefully.

High-quality evidence such as systematic reviews and meta-analyses on the benefits and harms of alternative treatment options is required to improve patient outcomes. An American review by Cooper et al. recently analyzed the knowledge gaps in the current literature concerning

TEs. As only 11% of the studies were relevant to evidence-based practice, current otolaryngologic research lacks strong evidence on the clinical practice guidelines of TEs[16]. This commentary considered studies from a wide variety of countries to ensure an international consensus. The medical literature was assessed by relevance to this commentary. Forward reference searching from the Byars et al. article was used to find studies that further examined the risk posed by TEs.

Table 1. Paradise Criteria, an evidence-based approach to assess the need of tonsillectomies[5].

Criterion	**Definition**
Minimum frequency of sore throat episodes	At least seven episodes in the previous year, at least five episodes in each of the previous two years, or at least three episodes in each of the previous three years
Clinical features	Sore throat plus at least one of the following features qualifies as a counting episode: ● Temperature of greater than 100.9 degrees Fahrenheit ● Cervical adenopathy (tender lymph nodes or lymph node size greater than 2 cm) ● Tonsillar exudate ● Culture positive for group A B-hemolytic streptococcus
Treatment	Antibiotics administered in the conventional dosage for proved or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record If the episodes are not fully documented, subsequent observance by the physician of two episodes of throat infection with patterns of frequency and clinical features consistent with the initial history

Long-term implications of TEs and adverse effects

Novel evidence has indicated that TEs increase the risk of a wide variety of diseases. A recent cohort study done in Denmark was the first to evaluate the relationship between the long-term risks of allergic, infectious, and respiratory diseases in adults who underwent the removal of tonsils, adenoids, or adenotonsillectomies (ATEs) in the first nine years of childhood[17]. This population-based cohort followed 1,189,061 children born between 1979 and 1999. There were 60,667 surgical patients which included 17,460 AEs, 11,830 TEs, or 31,377 ATEs, who were compared to 1,157,684 controls. The data extracted from Danish registries covered 10-30 years of medical history and found a 17% increase in risk for allergic and infectious diseases in the ATE group (RR: 1.17; 95% CI: 1.10-1.25; n=37618; p-value<0.00064)[17]. Out of the 28 disease groups (such as infectious, inflammatory, circulatory, etc.), 78% of them had small but significant increases in relative risk after correcting for subgroup analyses. The most noteworthy

finding was that TEs led to a 2.72-fold increase in relative risk (RR: 2.72; 95% CI: 1.54-4.80; n= 22684; p-value<0.00064) compared to controls for the incidence of upper respiratory tract diseases[17]. These results concur with another study that indicated a 1.96-fold increase in the relative risk (RR: 1.96; 95% CI: 1.14-3.36; n=41; p-value=0.020) of asthma for adults who underwent AE/TE in their childhood[18]. The NNH was 5 for the TE group, meaning that one in five patients develops an upper respiratory tract disease. Furthermore, AEs were associated with a 2-fold increase in the risk (RR: 2.11; 95% CI: 1.53-2.92; n=701; p-value<0.00064) for chronic obstructive pulmonary disorder (COPD)[17]. Tonsils are lymphatic tissue that initiate immune responses through B-cell and T-cell lymphocytes to airborne antigens in the mouth and nose. They are also the most immunologically active between the ages of 3 and 10 years[19]. Therefore, removing tonsils can impair immune function and expose patients to respiratory diseases. There is a strong correlation between these surgeries and the incidence of respiratory diseases.

TEs are also associated with an increased risk for cancers. A German case-control study found a statistically significant OR of 1.4 (OR: 1.4; 95% CI: 1.0-1.9; n=136; p-value<0.05) of developing acute leukemia in children who had undergone TEs[20]. In addition, a Taiwanese nationwide cohort study concluded that TE patients had a significantly higher risk of developing cancer during their 3-year follow-up period (IRR: 1.54; 95% CI: 1.05-2.25; n=103; p-value<0.05)[21]. Moreover, an American case-control study that examined pre- and post-menopausal women uncovered a correlation between TEs and increased likelihood of breast cancer in premenopausal women (OR: 1.50; 95% CI: 1.08-2.08; n=169; p-value=0.02)[22]. A possible explanation is that tonsils produce immune cells and removing them may impair immunosurveillance[22]. As TEs have been repeatedly associated with a higher overall risk of developing cancer, overtreatment should be cause for caution.

TEs and AEs are also associated with developing inflammatory disorders. Studies have correlated TEs with an augmented risk for inflammatory bowel disease. A systematic review concluded that though there is no definitive association between TEs and ulcerative colitis, there is a positive relationship between TEs and Crohn's disease (OR: 1.37; 95% CI: 1.16-1.62; n=7666; p-value<0.05)[23]. Increased risk of appendicitis and sarcoidosis in adults has also been linked with TEs and AEs in foreign studies[24,25]. A Swedish cohort study found that adults and children who received a TE had a significantly increased standardized incidence ratio (SIR: 1.34; 95%CI 1.30-1.37; n=5357; p-value not reported) of developing autoimmune disorders[26]. Given the long-term effects and impaired quality of life experienced with these inflammatory disorders, it is important for practitioners to weigh the risk and benefit of TEs.

As there are a myriad of disorders including respiratory tract infections, cancers, and inflammatory disorders that correlate with these surgeries, it is valuable to explore alternatives.

Table 2. A summary of the studies examined and used in this section.

Studies				Findings	
Authors	**Population**	**Condition**	**Methods**	**Ratio**	**95% CI**
Byars et al.	Adults who underwent TEs or AEs in the first 9 years of their lives	Upper respiratory tract diseases	Population-based cohort	RR: 2.72	1.54-4.80
		Allergic and infectious diseases		RR: 1.17	1.10-1.25
		COPD		RR: 2.11	1.53-2.92
Yurtsever et al.	Adult with an average age of 42.5	Asthma	Retrospective cohort	RR: 1.96	1.14-3.36
Schüz et al.	Pediatric population (ages 0-14)	Acute leukemia	Case-control	OR: 1.4	1.0-1.9
Sun et al.	Adult population with and without tonsillectomy	Different cancers	Nationwide population-based cohort study	IRR: 1.54	1.05-2.25
Brasky et al.	Pre- and post-menopausal women	Breast cancer	Population-based case-control	OR: 1.50	1.08-2.08
Sun et al.	Adults from GI and outpatient clinics	Crohn's disease	Systematic review and meta-analysis	OR: 1.37	1.16-1.62

Reform to medical practice and education

Given the short and long-term adverse effects of TEs and that many are performed without sufficient clinical indication, healthcare providers need to re-evaluate their approach to TEs and also identify better alternatives. A retrospective chart review found that radiofrequency tissue volume reduction (RFTVR) reduced tonsil size by 86% while cold dissection removed 100% on average. However, the study found that the radiofrequency coblation group (n=50) experienced significantly fewer days of pain, reduced activity and required fewer days of medication compared to the cold dissection group (n=50; p-value<0.0001)[27]. RFTVR only requires local anesthesia, making it potentially less harmful than TEs which require general anesthesia. RFTVR also minimizes pain, with patients returning to normal function within two days of the procedure, unlike TEs for which the average recovery time is seven days[28]. Though this alternative was only tested in adults and its long-term effects have not been studied, it is a promising avenue that should be explored in the pediatric population as it can both prevent patient discomfort and increase quality of life in the short-term.

Currently, patients seek TEs as a preventative approach to avoid potential tonsillitis[6-8]. This mentality ultimately puts patients at unnecessary risk. Evidence-based protocols should be taught by educators and followed by healthcare providers to prevent overtreatment. In the case of TEs, overtreatment seems to be more harmful than beneficial for both the patients and the medical system in the long-term. To further curtail overtreatment, medical educators ought to emphasize the importance of assessing their necessity. Educational reform also needs to emphasize the importance of communicating risks. Physicians and specialists must be equipped to clearly communicate the short- and long-term risks to the patients and/or their guardians. According to a recent update to the American Clinical Practice Guideline on Pediatric TEs,

effective communication is identified as a quality improvement opportunity for physicians. It outlines that physicians can better communicate surgical and postoperative complications. This implies that there is room for improvement in the quality of communication between physicians and their patients. The guideline also notes that patient expectations can be improved through education. One of the major changes to the guideline was incorporating new evidence into practice and addressing patient opinions[29]. Patients must understand that what seems to be a prophylactic measure is, in reality, a major surgical procedure with risks and complications that can and should be avoided if possible. Hence, a tripartite approach to overtreatment could include improvements to patient education, establishing and following specific evidence-based protocols and considering alternate treatment plans.

Conclusions

Tonsillectomies continue to be recommended at alarming rates in Canada, especially amongst children. Though they could improve the quality of life in the short-term, novel findings suggest that TEs are correlated with multiple severe long-term morbidities and adverse outcomes. In order to mitigate these effects, less invasive alternatives should be explored while avoiding the saturation of invasive surgical procedures. Healthcare providers must effectively communicate risks associated with TEs and dispel them as a prophylactic measure. Evidence-based decision-making, such as the use of the Paradise criteria, is of paramount importance when assessing the need for TEs. Therefore, using clinical criteria outlining when TEs are necessary and investing in researching alternatives are recommended.

Abbreviations

1. TE - tonsillectomy
2. AE - adenoidectomy
3. ATE - adenotonsillectomy
4. PFAPA - Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis
5. RR - risk ratio or relative risk
6. NNT-harm - number needed to treat-harm
7. COPD - chronic obstructive pulmonary disorder
8. OR - odds ratio
9. IRR - incidence rate ratio
10. CI - confidence interval
11. SIR - standardized incidence ratio
12. RFTVR - radiofrequency tissue volume reduction

References

1. Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, Burns JJ, et al. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg. 2011 Jan 01; 144: S1–30.
2. Canadian Institute for Health Information. Inpatient hospitalizations, surgeries and newborn indicators [Internet]. Canada: CIHI; 2018. Available from: cihi.ca/sites/default/files/document/stats_dad_hmdb_ih_1314_en.xlsx
3. Burton MJ, Glasziou PP, Chong LY, Venekamp RP. Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database of Systematic Reviews. 2014 Nov 19; 1(11): CD001802.
4. Paradise JL, Bluestone CD, Colborn KD, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. Am Aca Peds. 2002 Jul 01; 110(1): 7-15.
5. Šumilo D, Nichols L, Ryan R, Marshall T. Incidence of indications for tonsillectomy and frequency of evidence-based surgery: a 12-year retrospective cohort study of primary care electronic records. Br J Gen Pract. 2018 Sept 07; 678: 33–41.
6. Woo J-M, Choi J-Y. Tonsillectomy as prevention and treatment of sleep-disordered breathing: a report of 23 cases. Maxillofac Plast Reconstr Surg. 2016 Nov 25; 38.
7. Bluestone CD. Current indications for tonsillectomy and adenoidectomy. Ann Otol Rhinol Laryngol. 1992 Jan 01; 101: 58–64.
8. Misiukiewicz K, Posner M. Role of prophylactic bilateral tonsillectomy as a cancer preventive strategy. Cancer Prev Res. 2015 Jul 01; 8: 580–582.
9. Wall JJ, Tay KY. Postoperative tonsillectomy hemorrhage. Emerg Med Clin North Am. 2018 May 01; 36: 415–26.
10. Lee MS, Montague ML, Hussain SS. Post-tonsillectomy hemorrhage: cold versus hot dissection. Otolaryngol Head Neck Surg. 2004 Dec 01; 131: 833-836.
11. Gendy S, O'Leary M, Colreavy M, Rowley H, O'Dwyer T, Blayney A. Tonsillectomy—cold dissection vs. hot dissection: a prospective study. Ir Med J. 2005 Nov 01; 98: 243-244.
12. O'Leary S, Vorrath J. Postoperative bleeding after diathermy and dissection tonsillectomy. Laryngoscope. 2009 Jan 03; 115: 591-594.
13. Johnson RF, Chang A, Mitchell RB. Nationwide readmissions after tonsillectomy among pediatric patients - United States. Int J Pediatr Otorhinolaryngol. 2018 Apr 01; 107: 10–3.
14. Muninnobpamasa T, Khamproh K, Moungthong G. Prevalence of tonsillectomy and adenoidectomy complication at Phramongkutklao Hospital. J Med Assoc Thai. 2012 May 01; 95 Suppl 5: S69-74.
15. Tomofuji S, Sakagami M, Kushida K, Terada T, Mori H, Kakibuchi M. Taste disturbance after tonsillectomy and laryngomicrosurgery. Auris Nasus Larynx. 2005 Dec 01; 32: 381–6.

16. Cooper CM, Checketts JX, Brame L, Gray H, Downs JB, Vassar M. An analysis of the literature addressing tonsillectomy knowledge gaps. Int Journal of Pediatric Otorhinolaryngology. 2018 Dec 01; 115: 89–93.
17. Byars SG, Stearns SC, Boomsma JJ. Association of long-term risk of respiratory, allergic, and infectious diseases with removal of adenoids and tonsils in childhood. JAMA Otolaryngol Head Neck Surg. 2018 Jul 01; 1;144(7):594–603.
18. Yurtsever N, Soyyigit S, Sozener ZC, Mungan D, Kose SK, Misirligil Z. Is adenoidectomy and/or tonsillectomy a risk factor for allergic diseases and asthma in adulthood? Eurasian J Med. 2018 Oct 01;50(3):152–5.
19. Ramos SD, Mukerji S, Pine HS. Tonsillectomy and adenoidectomy. Pediatr Clin North Am. 2013 Aug 01;60(4):793–807.
20. Schüz J, Kaletsch U, Meinert R, Kaatsch P, Michaelis J. Association of childhood leukaemia with factors related to the immune system. Br J Cancer. 1999 Apr 09;80(3–4):585–90.
21. Sun L-M, Chen H-J, Li T-C, Sung F-C, Kao C-H. A nationwide population-based cohort study on tonsillectomy and subsequent cancer incidence. Laryngoscope. 2015 Jan 01;125(1):134–9.
22. Brasky TM, Bonner MR, Dorn J, Marhsall JR, Vena JE, Brasure JR, et al. Tonsillectomy and breast cancer risk in the Western New York Diet Study. Cancer Causes Control. 2009 Apr 01;20(3):369–74.
23. Sun W, Han X, Wu S, Yang C. Tonsillectomy and the risk of inflammatory bowel disease: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2016 Jun 01;31(6):1085–94.
24. Sawahata M, Nakamura Y, Sugiyama Y. Appendectomy, tonsillectomy, and risk for sarcoidosis – A hospital-based case-control study in Japan. Respir Investig. 2017 May 01; 55: 196-202.
25. Ballester JC, Ballester F, Rubio EC et al. Association between tonsillectomy, adenoidectomy, and appendicitis. Rev Esp Enferm Dig. 2005 Mar 01;97: 179-186.
26. Ji J, Sundquist J, Sundquist K. Tonsillectomy associated with an increased risk of autoimmune diseases: A national cohort study. J Autoimmun. 2016 Jun 22; 72:1–7.
27. Friedman M, LoSavio P, Ibrahim H, Ramakrishnan V. Radiofrequency tonsil reduction: safety, morbidity, and efficacy. Laryngoscope. 2003 May 01;113(5):882–7.
28. Nelson LM. Radiofrequency treatment for obstructive tonsillar hypertrophy. Arch Otolaryngol Head Neck Surg. 2000 Jun 01;1131;126(6):736–40.
29. Mitchell RB, Archer SM, Ishman SL, Rosenfeld RM, Coles S, Finestone SA, et al. Clinical practice guideline: tonsillectomy in children (update)-executive summary. Otolaryngol Head Neck Surg. 2019 Feb 05;160(2):187–205.

Commentary

Resource stewardship in Canadian undergraduate medical education

Sahil Sharma and Matthew Rowe

Western University Schulich School of Medicine & Dentistry, London, Canada

Abstract

New research suggests Canadian physicians order more than 1,000,000 potentially unnecessary tests and treatments each year. Strategies to educate medical students about the CanMEDs Resource Stewardship directive and judicious testing practices can help the healthcare system manage fiscal stress and improve healthcare experiences for patients. This article outlines several strategies that can be implemented at the undergraduate medical education level through Choosing Wisely Canada's Students and Trainees Advocating for Resource Stewardship (STARS) program. The educational strategies feature group-based learning, lecture integration, and supportive online modules. Educating medical students across the country about judicious testing can produce the generation of resource-conscientious doctors that healthcare's increasingly tight budget demands.

Keywords: Healthcare quality improvement; patient safety; unnecessary procedures; Choosing Wisely

Corresponding author: Sahil Sharma, sshar68@uwo.ca

Introduction

There is a need for programs of resource stewardship to be implemented in medical education in order to improve the way healthcare is delivered in Canada. This article outlines methods of delivering resource stewardship education to medical students at the undergraduate level, specifically through Canada's Choosing Wisely program. Resource stewardship in medicine is defined as clinical practice that employs the most efficient options to care for a patient. It is medicine that focuses efforts toward necessary care and limits unnecessary care, thereby minimizing patient morbidity while making the most of limited resources.

New data suggests that unnecessary medical tests, procedures, and treatments are driving factors in the increased cost of health care in Canada.[1] The Canadian Institute for Health Information recently reported the use of more than 1,000,000 potentially unnecessary tests and treatments in Canada each year.[2] The problem of overuse is not confined to Canadian borders; rates of inappropriate antibiotic use are reaching 57% in China, and inappropriate hysterectomy rates in the United States (US) range from 16% to 70%.[3]

As part of the effort to address unnecessary interventions, Dr. Andrew Burke founded a program at McMaster University designed to teach students about resource stewardship: the Stewardship Curriculum and Audit for Residents to Cultivate Efficiency, or SCARCE program. SCARCE gave internal medicine residents feedback on their ordered tests and showed that 60% of these tests had little to no clinical utility.[4] Such testing can be costly; the National Academy of Medicine in the US (previously known as the Institute of Medicine) estimates that roughly $210 billion of the $750 billion spent on American healthcare in 2012 was put towards inappropriate care.[5] Unnecessary and inappropriate care can also cause physical and psychological harm to patients with limited benefit; this is particularly true in settings where palliative approaches are underutilized.[6,7] For example, unnecessary imaging may identify unrelated abnormalities, or 'incidentalomas', which can precipitate further unnecessary and often invasive investigations, and increase patient anxiety.[3] Particularly in end-of-life settings, it is not uncommon for patients to be subjected to admissions and treatments that afford little benefit.[8] Although Canadians do not have access to detailed healthcare spending data, as compared to US data, existing research establishes clear patterns of unnecessary medical treatments and procedures.[9–11]

This growing body of literature points to the need to improve stewardship of health care resources by changing clinical practice. Research suggests that interventions to improve resource stewardship during training have a lasting effect in practice.[12] Medical education and training afford unique opportunities to impress upon future physicians the burden of unnecessary treatment on the health care system, and the potential to improve patient care through better resource stewardship. The updated CanMEDS 2015 physician competency framework reflected the rising importance of this issue by adding "Resource Stewardship" to the Leader competency.[13] Resource Stewardship in medical education is one focus of the Choosing Wisely Canada (CWC) campaign, which has initiated programs to raise awareness about the harms of unnecessary care.[14]

The CWC ultimately seeks to facilitate patient-physician conversations about unnecessary care. It enlists national medical specialty societies to develop recommendations of 'Things Clinicians and Patients Should Question'.[15] Several professional societies from a wide range of specialties, such as Anaesthesia, Emergency Medicine, and General Surgery have all contributed recommendations relevant to their field. They identify tests and treatments that are commonly used but are not supported by evidence and pose potential harms.[16] By publicizing these lists, CWC promotes discourse and supports clinical staff and patients alike in having resource-conscientious care discussions.

Outside of the clinic, CWC educates experts, learners, and the general population through multimedia resources and live conferences to raise awareness about the harms of unnecessary care. With medical students, CWC aims to foster local student leadership in support of the campaign through the Students and Trainees Advocating for Resource Stewardship (STARS) program.[17] The STARS program engages passionate medical student leaders across the country and equips them with the tools to increase awareness and advocate for more curricular content on resource stewardship at their schools. Since the program's inception in November 2015, initiatives led by STARS students have reached over 2000 Canadian medical students.[18] Below are strategies which medical student leaders can implement through STARS at Canada's 17 medical schools.

Group based learning

Many Canadian medical school curricula include formal small group learning sessions between a few students and a subject expert. The small-group sessions usually pair case studies to a teaching block's lecture learning, giving medical students a chance to consolidate new knowledge through patient histories, symptom assessments, diagnostic approaches, and therapies. Resource stewardship principles can be incorporated into the diagnostic approach and therapy arms of the case studies.[19] Students should be encouraged to consider resource stewardship of tests, treatments, and procedures for each case study. This will enrich their understanding of the practical applications and scenarios associated with unnecessary care in the clinical setting.

Lecture integration

Resource stewardship should also feature in lectures, where students are often being exposed to diagnostic pathways and therapies for the first time. Increasing novel imaging modalities in medicine have simplified the visualization of disease. For example, when learning about valvulopathies during a cardiology block, the use of Doppler echocardiography provides an excellent visual aid to observe shifting blood flow and the movement of a diseased valve. However, when students are always shown an echocardiography image in lecture, they may start to assume that every cardiac issue must be accompanied by an echocardiogram. This bias can

hinder a student's ability to think creatively about the cases they see in small group or clinic and can teach technology dependence. Including CWC recommendations into lectures can promote critical thinking and serve as a reminder that not all cases merit certain diagnostics. Introduction of resource stewardship material in pre-clerkship education through lecture integration can bolster student confidence in creating management plans that exhibit resource stewardship.[20]

Online modules

The CWC offers online resource stewardship learning modules to all Canadian medical students. To encourage engagement with the modules, Canadian medical schools can offer their students certificates for completing the modules, which would serve to demonstrate student competency on the topic of resource stewardship. The modules serve as independent learning resources but can also be structured around pre-existing curricula to teach medical students about resource stewardship, such as the Open School course on quality, value, and cost in health care offered by the Institute of Health Care Improvement.[21] Stewardship modules can also be handpicked to align with a given medical school's values and learning goals. Module teaching for improving resource stewardship has been shown to be effective; an initiative implemented to teach stewardship in rheumatology was successful in teaching total costs and time associated with trainees' diagnostic choices. Such modules were shown to be positively received and served as an effective tool in teaching resource stewardship in the approach to rheumatology patients.[22]

Extra-curricular advocacy

Students can carry their advocacy for resource stewardship beyond the classroom and into extra-curricular initiatives. Several students have already taken up extra-curricular advocacy regarding CWC principles through on-campus speaker series, conferences, and awareness weeks to educate curriculum committees and medical students.[23] In addition to organizing on-campus events, CWC students can and have published articles in school journals regarding the importance of resource-conscious patient care to promote awareness among readers.[24]

Conclusion

Physicians are the main responsible body for decisions regarding healthcare resource use, as they fill the role of healthcare provision managers. As such, physician decision-making has been estimated to drive nearly 80% of all health care costs.[1] We are uniquely positioned to minimize waste in health care and to maximize the value of limited health resources by engaging in conversations about resource stewardship in the clinic and the classroom. The CWC's speciality-specific lists of "Things Clinicians and Patients Should Question" empowers patients and health care providers alike to improve health care. Additionally, incorporating CWC

materials into lectures, small group learning environments, online modules, and other extra-curricular modalities empowers medical students to practice wisely in the future.

References

1. Drivers of health care costs [Internet]. The Physicians Foundation; 2017 [cited 2017 Mar 29]. Available from: https://physiciansfoundation.org/wp-content/uploads/2017/12/Drivers_of_Health_Care_Costs_-_November_2012.pdf
2. Unnecessary care in canada: technical report. [Internet]. Canadian Institute for Health Information; 2017 [Cited 2017 Mar 29]. Available from: https://www.cihi.ca/sites/default/files/document/choosing-wisely-baseline-report-en-web.pdf
3. Brownlee S, Chalkidou K, Doust J, Elshaug AG, Glasziou P, Heath I, et al. Evidence for overuse of medical services around the world. The Lancet [Internet]. 2017 Jan 8 [cited 2017 Jun 4]. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32585-5/abstract
4. How do you teach residents to allocate finite resources? [Internet]. The ICRE Blog; 2013 [cited 2017 Mar 29]. Available from: https://icreblog.royalcollege.ca/2013/01/18/how-do-you-teach-residents-to-allocate-their-finite-resources/
5. Smith M, Saunders R, Stuckhardt L, McGinnis JM, editors. Committee on the Learning Health Care System in America, Institute of Medicine. Best care at lower cost: the path to continuously learning health care in America [Internet]. Washington (DC): National Academies Press (US); 2013 [cited 2017 Jun 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK207225/
6. Gaertner J, Wolf J, Voltz R. Early palliative care for patients with metastatic cancer. Current opinion in oncology. 2012 Jul 1;24(4):357-62.
7. Lauzier S, Maunsell E, Levesque P, Mondor M, Robert J, Robidoux A, et al. Psychological distress and physical health in the year after diagnosis of DCIS or invasive breast cancer. Breast Cancer Res Treat. 2010 Apr;120(3):685–91.
8. Cardona-Morrell M, Kim JCH, Turner RM, Anstey M, Mitchell IA, Hillman K. Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem. Int J Qual Health Care. 2016 Sep 1;28(4):456–69.
9. Palda VA, Bowman KW, McLean RF, Chapman MG. "Futile" care: Do we provide it? Why? A semistructured, Canada-wide survey of intensive care unit doctors and nurses. J Crit Care. 2005 Sep;20(3):207–13.
10. Hol L, Sutradhar R, Gu S, Baxter NN, Rabeneck L, Tinmouth JM, et al. Repeat colonoscopy after a colonoscopy with a negative result in Ontario: A population-based cohort study. CMAJ Open. 2015 Jun 17;3(2):E244–50.
11. Lakhani A, Lass E, Silverstein W. Less is More: Integration of resource stewardship in medical education. Montreal: Canadian Federation of Medical Students. 2016.

12. Sirovich BE, Lipner RS, Johnston M, Holmboe ES. The association between residency training and internists' ability to practice conservatively. JAMA Intern Med. 2014 Oct;174(10):1640–8.
13. CanMEDS 2015 OTR Special Addendum [Internet]. Royal College; 2016 [updated 2016 Dec 6; cited 2017 Mar 29]. Available from: http://canmeds.royalcollege.ca/uploads/en/framework/CanMEDS%202015%20OTR_Special_Addendum_EN.PDF
14. Leon-Carlyle M, Srivastava R, Levinson W. Choosing Wisely Canada: integrating stewardship in medical education. Acad Med. 2015 Nov;90(11):1430.
15. Patient Resources [Internet]. Choosing Wisely Canada; 2017 [cited 2017 Mar 29]. Available from: http://www.choosingwisely.org/doctor-patient-lists/
16. Recommendations [Internet]. Choosing Wisely Canada; 2019 [cited 2019 Apr 30]. Available from: https://choosingwiselycanada.org/recommendations/
17. Vogel L. Medical students now choosing wisely. CMAJ. 2016 Jan 5;188(1):17–17.
18. Medical Students Choose Wisely - Costs of Care [Internet]. Costs of Care; 2018 [cited 2019 Mar 29]. Available from: http://costsofcare.org/medical-students-choose-wisely/
19. Wishart E, Pendrith C, Eppler K, Cheng EJ. A233 implementing resource stewardship into undergraduate medial education: Choosing Wisely Canada. Journal of the Canadian Association of Gastroenterology. 2018 Mar 1;1(suppl_2):343–343.
20. P046: A quality improvement initiative for improving integration of resource stewardship concepts into undergraduate medical education [Internet]. Canadian Journal of Emergency Medicine | Cambridge Core; 2019 [cited 2019 Mar 20]. Available from: https://www.cambridge.org/core/journals/canadian-journal-of-emergency-medicine/article/p046-a-quality-improvement-initiative-for-improving-integration-of-resource-stewardship-concepts-into-undergraduate-medical-education/727BF65AEC44FF8CFEF675E52F738376
21. QCV 100: An introduction to quality, value, and cost in health care [Internet]. Institute for Healthcare Improvement Open School; 2017 [cited 2019 Apr 30]. Available from: http://www.ihi.org/education/IHIOpenSchool/Courses/Documents/SummaryDocuments/QCV%20100%20SummaryFINAL.pdf
22. Zhou LL, Tait G, Sandhu S, Steiman A, Lake S. Online virtual cases to teach resource stewardship. The Clinical Teacher [Internet]. 2018 Jun 11 [cited 2019 Mar 20]; Available from: http://doi.wiley.com/10.1111/tct.12804
23. National Capital Conference on Emergency Medicine (NCCEM) [Internet]. University of Ottawa; 2017 [cited 2017 Jun 4]. Available from: http://www.med.uottawa.ca/cme/assets/documents/events/NCCEM2017_Brochure%20Draft_V4_Oct%2031.pdf
24. Muntyanu A, Jebanesan D, Kuling P. Choosing Wisely: resource stewardship education in canadian medical schools. University of Ottawa Journal of Medicine [Internet]. 2017 Jan 23 [cited 2017 Jun 4];7(1).