Original Research
Assessment of rural colonoscopy wait times, quality, and safety

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THE McMaster University Medical Journal (MUMJ) was established in 2003 to share advances in medicine, augment our understanding of the social issues impacting individual and population health, and encourage the discussion of ethical and legal issues as they apply to the profession. Our mandate is to share bright ideas in science and medicine that are relevant to our McMaster readers, as well as the wider medical community, and we publish work by medical and graduate students from across Canada.

The 15th volume of MUMJ includes a broad array of original research, commentary pieces, and review articles. Our authors outline the usefulness of simulation training in improving pediatric trauma care, delve into the role of mentorship in medical school, and examine how growing up alongside a sibling with a chronic disease can shape one’s civic views. They challenge the effectiveness of Ontario’s approach to osteoporosis prevention, examine the safety and utility of colonoscopies in rural areas, and argue for more exposure to bariatric care during medical training.

MUMJ is proud to continue our relationship with McMaster Medical Student Research Day (MMSRD). This annual event allows medical students to present their work, learn about the research being done by their peers, and network with staff and fellow students. In our current issue, we have included the winning abstracts from this year’s MMSRD event.

I am exceptionally grateful to the editorial board, staff advisors, and administrative staff who have generously contributed their time and hard work to this volume of MUMJ. Thank you to our authors for giving us the opportunity to publish your work – it enriches our understanding of science and medicine, prompts us to reflect on our medical learning, and galvanizes us to improve the care we offer our patients.

Readers, thank you for your interest in our journal. I hope you enjoy reading this issue of MUMJ as much as we have enjoyed preparing it.

Elizabeth Simms  
Editor-in-Chief  
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Assessment of rural colonoscopy wait times, quality, and safety

Authors:
Fraser Kegel¹, BHSc, BFsc
Emma Wallace¹, BHSc, BSc
Darrell Baker², MD, FRCSC, FACS

Author Affiliations:
1. McGill University School of Medicine, Montreal, Quebec, Canada
2. McMaster University, Hamilton, Ontario, Canada

ABSTRACT:

Introduction: Although colonoscopies performed in rural settings have been shown to be safe and of high quality, screening occurs less frequently among these populations than in urban centres and colorectal cancer rates are higher. The aim of this study was to evaluate the wait times, quality, and safety of colonoscopies performed by a single endoscopist in a rural Ontario hospital and to determine whether any patient and operative factors were associated with higher relative risks of discovering a pathology during colonoscopy.

Methods: This was a prospective, observational study examining consecutive patients undergoing colonoscopy in a rural setting for any indication over a five-month period. Patient demographic information, referral methods and wait times, colonoscopy indication, procedural findings and timing, adenoma detection rates (ADR), polypectomy detection rates (PR), cecal intubation rates (CIR), and complication rates were collected from medical records at the Haldimand War Memorial Hospital.

Results: A total of 222 patients were included. Median patient wait times were 57 days for patients with symptoms concerning for colorectal cancer. The CIR was 96.7%. Inadequate bowel preparation was observed in 2.3% of patients. The ADRs and PRs varied from 4.4-30.0% and 8.9-40.0%, respectively, depending on patient risk category. There were no complications of bowel perforation or postoperative hemorrhage. A colonoscopy withdrawal time of greater than six minutes was associated with higher PR (RR = 13.4, 95% CI [7.77, 23.1], p < 0.001) and higher ADR (RR = 19.0, 95% CI [9.78,36.7], p < 0.001). Finally, there were no significant differences in PR (p = 0.66), ADR (p = 0.64), CIR (p = 0.58), mean total colonoscopy time (p = 0.64), or mean colonoscopy withdrawal time (p = 0.16) between patients who underwent procedures earlier in the operating room schedule compared with later in the day.

Conclusion: We demonstrate that rural colonoscopies continue to be safe, effective, and high-quality procedures. We also show that patient wait times for rural colonoscopies are within the established recommendations.

Keywords: rural, colonoscopy, colorectal cancer screening, colonoscopy withdrawal time
**INTRODUCTION**

Colorectal cancer (CRC) is the second most common cause of cancer mortality for both men and women. Screening for CRC decreases deaths from such malignancies. In Ontario, current guidelines involve screening patients for colorectal cancer at the age of 50 with either fecal occult blood testing (FOBT) or colonoscopy depending on patient risk-profile. Colonoscopy is an effective screening method because it can both detect and remove pre-malignant and malignant lesions during the same procedure; as a result, demand for CRC screening with colonoscopy is increasing. Despite this, rural populations are screened less than urban populations and may face more barriers (such as longer distance to care and decreased number of physicians) to screening with colonoscopy. The rates of CRC seem to be higher in areas where there are fewer physicians capable of offering screening colonoscopies. Thus, there is a need for increased CRC screening in rural locations, especially because rural colonoscopies have been demonstrated to be safe and meet the quality indicators established by Cancer Care Ontario (CCO).

Quality indicators currently supported by CCO for colonoscopies include a cecal intubation rate (CIR) of ≥ 95% for patients with adequate bowel preparation and no obstructive lesions, a hospitalization rate of ≤ 1% resulting from post-polypectomy bleeding, and a bowel perforation rate of ≤ 0.1%. Endoscopists are encouraged to record additional auditable statistics including adenoma detection rate (ADR), polypectomy rate (PR), colonoscope withdrawal time, post-colonoscopy colorectal cancer (PCCRC), and quality of bowel preparation; however, these statistics are not supported by specific numeric benchmarks.

Recommendations for the maximum acceptable patient wait times have been established for various patient groups. CCO recommends that patients with a family history of colorectal malignancy receive a colonoscopy within 182 days of referral. In addition, The Canadian Association of Gastroenterology (CAG) and CCO recommend that patients presenting with the following be evaluated with an endoscopic examination within two months: symptoms of bright red blood per rectum (BRBPR), a change in bowel habits, iron-deficiency anemia, a positive FOBT, a positive fecal immunochemical test (FIT), a physical examination, or radiological findings suspicious for colorectal malignancy.

This study was conducted to evaluate the wait times, quality, and safety of colonoscopies performed by a single endoscopist at the Haldimand War Memorial Hospital (HWMH), a rural Ontario location. We also sought to determine whether any patient and/or operative factors were associated with higher relative risks of discovering a pathology during colonoscopy.

**METHODS**

This was a prospective, observational study conducted at the HWMH. Data was collected from consecutive patients who underwent colonoscopy for any reason over a five-month period in 2016. Patient demographic information including age, sex, method of referral, and indication for colonoscopy was collected. A review of the referral, consultation, and procedure dates was conducted to determine individual patient wait times. Colonoscopy indications were broadly categorized as screening, surveillance, symptomatic, or other. Screening colonoscopies were defined as colonoscopies performed on patients between 50-74 years-of-age referred for their first colonoscopies, to further investigate a positive FOBT, or for a family history of colorectal cancer. Surveillance colonoscopies were defined as colonoscopies performed on patients to follow-up previous detection and removal of a colorectal polyp or previous colonoscopy. Several subgroups within these categories were also defined. If a patient was referred for multiple indications, a review of the referral...
and consultation records was conducted to elucidate the single, most relevant indication.

Findings recorded during the colonoscopy procedure included hemorrhoids, diverticulosis (presence or absence and colonic location), and lesions (polyps and masses). Pathological diagnoses were recorded for each lesion. PR (proportion of patients with one or more polyps identified and removed during colonoscopy) and ADR (proportion of patients with one or more adenomatous polyps identified and removed during colonoscopy) were recorded for all patient subgroups. Bowel preparation was recorded as good (no or minimal liquid stool that could be easily cleared), fair (collections of semisolid stool that could not be easily cleared), or poor (semisolid or solid debris that could not be completely cleared). Cecal intubation was confirmed by direct visualization of the cecum and ileocecal valve or by ileal intubation and CIR was recorded. Complication rates of bowel perforation and hemorrhage were also collected. Individual procedural and withdrawal times were recorded and compared to the current recommended standard of care. Students t-tests were used to calculate discrete variables and relative risks were calculated to determine if any patient or operative factors were associated with an increased risk of discovering a pathological lesion.

RESULTS
A total of 222 patients (54.5% female) with a mean age of 64 (95% CI [62.5, 65.6], range 28 – 90) were included in this study. Patients were referred from general practitioners (64.4%), scheduled directly following previous colonoscopies (30.2%), or referred from specialists (4.5%). There was a total of 72 (32.4%) screening colonoscopies, 48 (21.6%) surveillance colonoscopies, 98 (44.1%) colonoscopies for symptomatic patients, and 2 (0.9%) colonoscopies that were performed as a part of a preoperative workup (Table 1). The median patient wait times were 63 days for all indications, 70 days for all screening colonoscopies, 32 days for referrals after a positive FOBT, 83 days for patients with a family history of colorectal cancer, and 57 days for patients with symptoms concerning for colorectal cancer (Table 2).

The most common finding on colonoscopy was diverticulosis (56.8%) (Table 3). Hemorrhoids were found in 23 patients (10.4%) and polyps were identified in 34 patients (15.3%). The most common pathological diagnosis of polyps was adenoma (79.3% of all polyps). Colonic adenocarcinomas were found in two patients (0.9%) who were undergoing their first colonoscopies. One patient was a 76-year-old male presenting with anemia and the other patient was a 63-year-old female referred for a screening colonoscopy. The ADR varied between 4.4 and 30.0%, and the PR varied between 8.9 and 40.0%, depending on patient risk category (Table 4).

The CIR was 96.7%. Inadequate bowel preparation was observed in 8 patients (2.3%). The mean withdrawal time was 5 minutes. There were no cases complicated by bowel perforation or post-operative hemorrhage (Table 4).
Patients who underwent a colonoscopy ≥ 20 minutes had a much higher chance of having a polyp (RR = 12.7, 95% CI [7.71, 20.9], \( p < 0.001 \)) or adenoma (RR = 14.0, 95% CI [7.04, 27.6], \( p < 0.001 \)) detected (Table 5). A colonoscopy withdrawal time ≥ six minutes was also associated with higher polyp (RR = 13.4, 95% CI [7.77, 23.1], \( p < 0.001 \)) and adenoma (RR = 19.0, 95% CI [9.78, 36.7], \( p < 0.001 \)) detection rates. Furthermore, patients who underwent a colonoscopy with a withdrawal time ≥ seven minutes were more likely to have a polyp (RR = 12.7, 95% CI [7.70, 20.8], \( p < 0.001 \)) or adenoma (RR = 15.3, 95% CI [8.31, 28.1], \( p < 0.001 \)) detected. Age ≥ 75, bowel preparation graded as good, and colonoscopy indication for surveillance of previously identified polyps were patient factors not associated with higher adenoma or polyp detection rates.

We were also interested in comparing the quality of colonoscopies conducted later in the daily operating room schedule to those performed earlier in the day. There were no significant differences in PR (\( p = 0.66 \)), ADR (\( p = 0.64 \)), CIR (\( p = 0.58 \)), mean total colonoscopy time (\( p = 0.64 \)), or mean colonoscopy withdrawal time (\( p = 0.16 \)) between colonoscopies completed earlier in the operating room schedule and those completed later.

**DISCUSSION**

In this study, patients were referred for colonoscopy to investigate symptoms concerning for colorectal malignancy more often than to screen for CRC. This may be attributed to rural barriers to health care and the increased use of FOBT for CRC screening in these settings. It may also draw attention to the need for increased awareness about screening colonoscopies in rural locations, where screening occurs less than in urban areas\(^5\)\(^-\)\(^13\).

The CCO and CAG have proposed recommendation for maximum patient wait times for screening and symptomatic endoscopic evaluation. In this study, median wait times for all indications were shorter than the recommendations; thus, rural colonoscopies may be performed without prolonged wait times. The CCO has not established benchmark values for ADR and PR because highly variable statistics have been reported across the literature\(^4\). Current ADRs range between 14.2 and 27.4% in urban centres and between 15.4 and 46% in rural facilities\(^5\)\(^-\)\(^6\)\(^,\)\(^17\)\(^-\)\(^19\). This wide range is likely due to the variability between indications for colonoscopy among studies and differing mean ages in the study populations\(^1\). This study found an above-average ADR in patients referred for colonoscopy for investigation of a positive FOBT while the ADR in the population undergoing first-time screening colonoscopies was slightly below those documented in previous literature. There was a surprisingly low ADR for the patients with a family history of colorectal cancer undergoing colonoscopy that may have resulted from information error when patients presenting with unclear or questionable family history of colorectal cancer.

When compared to academic endoscopists, rural endoscopists practice in more resource-limited settings, which may form a barrier to care for rural patients. Higher quality endoscopic equipment may allow for higher ADRs. For example, higher ADRs have been reported when high-definition colonoscopy was used\(^2\). The increased use of narrow-band imaging may result in lower PRs. In resource-limited settings, endoscopists may more often rely on optical diagnoses of polyps using narrow-band imaging more often due to limited resources (e.g., budget, assistants, equipment) as optical diagnoses have been reported to be 93% accurate in one study\(^21\). There also may be lower awareness for colorectal cancer screening in rural areas, so community initiatives to increase patient awareness for colorectal cancer screening may be useful.

**Table 4. Colonoscopy quality indicators and auditable statistics**

<table>
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<tr>
<th>Quality indicator</th>
<th>Cancer Care Ontario</th>
<th>Current study</th>
</tr>
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<tbody>
<tr>
<td>Cecal intubation rate</td>
<td>( \geq 95% )</td>
<td>96.7%</td>
</tr>
<tr>
<td>Perforation rate</td>
<td>( \leq 0.1% )</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hemorrhage rate</td>
<td>( \leq 0.1% )</td>
<td>0.0%</td>
</tr>
<tr>
<td>Auditable Statistic</td>
<td>Cancer Care Ontario</td>
<td>Current Study</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Adenoma detection rate</td>
<td>Variable</td>
<td>4.4 – 30.0%</td>
</tr>
<tr>
<td>PR</td>
<td>Variable</td>
<td>8.9 – 40%</td>
</tr>
<tr>
<td>Withdrawal time</td>
<td>N/A</td>
<td>5 minutes</td>
</tr>
<tr>
<td>PCCRC</td>
<td>Variable</td>
<td>0.0%</td>
</tr>
<tr>
<td>Inadequate bowel preparation</td>
<td>( \leq 10% )</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

**Table 5. Risk factors for higher adenoma or polypectomy rates during colonoscopy**

<table>
<thead>
<tr>
<th>Patient or procedural factor</th>
<th>Higher ADR</th>
<th>Higher PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>0.75</td>
<td>0.28-2.03</td>
</tr>
<tr>
<td>Colonoscopy ≥ 20 minutes</td>
<td>12.70</td>
<td>7.71-20.9</td>
</tr>
<tr>
<td>Withdrawal time ≥ 7 minutes</td>
<td>12.70</td>
<td>7.70-20.8</td>
</tr>
<tr>
<td>Withdrawal time ≥ 6 minutes</td>
<td>13.40</td>
<td>7.77-23.1</td>
</tr>
<tr>
<td>Bowel preparation graded as good(^1)</td>
<td>0.64</td>
<td>0.21-1.97</td>
</tr>
<tr>
<td>Surveillance for previous polyps(^2)</td>
<td>1.20</td>
<td>0.58-2.47</td>
</tr>
</tbody>
</table>

ADR: adenoma detection rate, PR: polypectomy rate, RR: relative risk, CI: confidence interval, \(^1\)Bowel preparation graded as good indicates no or minimal liquid stool that could be easily cleared, \(^2\)Colonoscopy indication was surveillance for previous polyps.
CIR is an important measure of colonoscopy quality because right-sided colorectal cancers are more likely to be missed than more distal lesions. The CIR in this study was well above the CCO recommendation of 95%. Based on the CCO quality indicators of colonoscopy complications, we show that rural colonoscopies are safe and of high quality. Missed lesion rate and history of prior colonoscopy with polypectomy are two of the strongest risk factors for early or missed colorectal cancers. Due to the duration of this study, the PCCRC rate was not evaluated.

Although the CCO colonoscopy guidelines do not include a specific colonoscopy withdrawal time as an auditable statistic for colonoscopy quality, many studies have demonstrated that longer withdrawal times are associated with higher rates of polypectomy and adenoma detection rates. In a 2014 large database study (N = 7972), Butterfly et al. reported higher rates of adenoma and clinically significant serrated polyp detection for colonoscopy withdrawal times longer than six minutes. In a community hospital, the polyp detection rate (PDR) was also significantly higher in colonoscopies with withdrawal times of greater than six minutes (20.9% vs. 48.3%, \( p \leq 0.01 \)) as reported by Baker et al. in 2015. This was reinforced in a recent 2017 cohort study (N = 878) by Kashiwagi et al., in which withdrawal times longer than 6 minutes were associated with a greater PDR, most significantly in the transverse and sigmoid colon with 2.3 (\( p = 0.004 \)) and 2.1 (\( p = 0.001 \)) times higher PDRs, respectively. This study has provided further evidence that colonoscopy withdrawal times \( \geq 6 \) minutes six and seven minutes at a community hospital result in higher polypectomy and adenoma detection rates. Colonoscopies \( \geq 20 \) minutes also yielded higher polypectomy and adenoma detection rates; however, it is possible that these longer colonoscopy times resulted from the longer withdrawal times and may not be as significant.

We also wanted to ensure that temporal factors did not influence the safety and quality of endoscopic procedures in resource-limited colonoscopy settings. We found no significant differences in PR, ADR, CIR, and colonoscopy withdrawal time between procedures conducted earlier in the operating room schedule compared with those conducted later.

This study was conducted in a rural centre by a single endoscopist, and thus is limited by low patient volumes. Lower volume limits the power of this study due to the number of strata necessary to classify patients according to risk of CRC and indication for colonoscopy. Due to the study length, PCCRC was not calculated. This study was strengthened by its prospective nature and the lack of colonoscopy technique variability, since a single endoscopist performed all procedures.

**CONCLUSION**

We have shown that patient wait times for colonoscopies within this rural setting are within the established CCO and CAG recommendations, and that these continue to be safe, effective, and high-quality procedures. In agreement with previous reports, we have demonstrated that withdrawal times \( \geq 6 \) minutes yield higher polypectomy and adenoma detection rates. The safety and quality of procedures performed later in the operating day did not significantly decrease compared with those performed earlier. Improved provincial screening for colorectal cancer has increased the demand for colonoscopies in both rural and urban settings. Although there are fewer endoscopists practicing rural, these findings may suggest that rural locations can accommodate these higher volumes as current standards are being met. Rural patients are underserved with regards to CRC screening; thus, community initiatives may have the potential to increase health care promotion and improve health outcomes in rural settings.

**References**

ABSTRACT:

Background: The morbidity and mortality of acute myocardial infarction (AMI) is dependent upon time to diagnosis and treatment. Delays to early diagnosis in the emergency department (ED) can have important clinical impact. We sought to determine whether ED patients with chest pain who arrived by self-transport to a Hamilton emergency department experienced a significant delay in door-to-electrocardiogram (DTE) and door-to-troponin (DTT) times compared to patients with chest pain that arrived by emergency medical services (EMS).

Methods: We randomly selected 1,000 charts from the over 13,000 visits with “cardiac chest pain” as the chief complaint at two EDs in the city of Hamilton in 2013. We divided these patients into two groups: those arriving by EMS and those arriving by self-transport. We then compared these two groups with respect to mean sex, age, DTE and DTT times.

Results: The self-transport group had a significantly longer door-to-troponin time (mean 4260 seconds) than the group that arrived via EMS (mean 3000 seconds) (p<0.001) and both groups had comparable DTE times. The nationally recommended benchmark was met for DTT time for the group that arrived via EMS, but not for the self-transport group. Recommended benchmarks for DTE times were not met, regardless of mode of arrival.

Conclusion: There was a significant difference in mean DTT times between patients who arrived to the ED via self-transport, versus patients who arrived via EMS. This study also revealed that the two EDs studied were not meeting the recommended benchmark times of ten minute DTE time.

INTRODUCTION

Acute myocardial infarction (AMI) contributes significantly to adult morbidity and mortality. Both increase with delays to definitive treatment such as percutaneous coronary intervention (PCI) and thrombolysis. The catch-phrase “time is muscle” expresses the impact of expediency upon limiting myocardial injury, and benchmarks for door-to-balloon (PCI) and door-to-needle time (thrombolysis) have been set at 90 and 30 minutes respectively. Diagnosis of AMI is an independent precursor to definitive treatment and, in patients with ischemic cardiac symptoms, can be made with electrocardiographic (ECG) findings alone. Door-to-ECG time (DTE) has become a benchmark for assessing quality of emergency department (ED) care for patients who present with chest pain as prolonged DTE times are associated with increased adverse outcomes in AMI patients. To that end, the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend a DTE time of less than ten minutes. Similarly, in patients with ischemic cardiac symptoms, cardiac troponin (cTn) levels alone can be diagnostic for unstable...
angina/non ST-elevation myocardial infarction\textsuperscript{4,16}. The AHA and ACC both recommend an initial door-to-troponin (DTT) results time of 30-60 minutes or less\textsuperscript{14}. Just as the door-to-balloon and door-to-needle times are dependent upon the DTE and DTT results time\textsuperscript{17}, the latter might also be affected by precursor variables. The door-to-needle or door-to-balloon time has been shown to be significantly shorter for AMI patients arriving by emergency medical services (EMS) than those arriving by self-transport\textsuperscript{16,19}. Hence, mode of arrival to the ED has the potential to affect DTT and DTE times. Because the 50-60\% of patients with chest pain arriving via EMS do not necessarily undergo the same ED entry processes as those arriving via self-transport, they are less likely to experience DTE delays\textsuperscript{2,4,18}. It is not known whether mode of transportation affects DTT similarly. Therefore, the primary objective of this study is to determine if patients presenting to the ED with cardiac chest pain experience differences in DTE and DTT times depending on mode of arrival.

METHODS

Data Collection

After receiving approval from the research ethics board, we created a password protected, encrypted database of all ED visits in the 2013 calendar year to two EDs in a Canadian city (Hamilton, ON). Our inclusion criteria were: adults (\geq 18 years old) and presenting with a Canadian Emergency Department Information Systems (CEDIS) standardized presenting complaint of chest pain with cardiac features. We then used a computer-generated random number generator to select 1000 charts for review. Two trained data abstractors independently conducted the chart reviews and data collection using a protocol and procedure manual in the same session. An initial sample batch of 100 chart reviews was checked for consistency by a third researcher to ensure compliance and agreement but was not included in the study collection of 1000 charts.

From the 1000 charts, researchers manually collected descriptive data for each subject: ED site, age, mode of arrival, DTE time, DTT time, sex, and Canadian Triage Acuity Scale (CTAS) score. The DTE and DTT times used the time of patient registration (triage) as the ‘door’ time as this was the time of first contact with the hospital and was recorded electronically. It was therefore taken as a consistent and accurate record of arrival time\textsuperscript{20}. The DTE time was the time recorded on the patients’ first ECG, and the DTT time used was the sample collection time recorded by nursing staff.

Data Analysis

We compared the two groups, arrival by EMS and arrival by self-transport, with respect to mean sex, age, DTE and DTT times. We compared the proportion of males and females using the Chi Square Test. We tested age, DTE time and DTT time for normality by the Shapiro-Wilk Test and assessed the differences in median rank of age, DTE and DTT times between groups with the Mann Whitney U Test. We conducted all analyses using SPSS (SPSS Inc. Version 18, Chicago. IL).

Table 1.

| Baseline Characteristics: Median Age in Self-Transport vs EMS Groups |
|-----------------|-----------------|-----------------|-----------------|
| Characteristic  | Self-Transport  | EMS             | Difference in Medians |
| Age (years)     | 58              | 65              | 7               |
| 95\% Confidence Interval | 3.86, 10.14      | <0.001          |

Table 2.

| Baseline Characteristics: % of Participants in Self-Transport vs EMS Groups by Sex |
|-----------------|----------------|-----------------|-----------------|
| Sex             | Self-Transport | EMS             | P-value         |
| Male            | 345 (53.2\%)   | 176 (50.0\%)    | 0.327           |
| Female          | 303 (46.8\%)   | 176 (50.0\%)    |                 |

Note: $\chi^2 = 0.96, df = 1$.

Table 3.

| Median Door To Troponin Draw and ECG Completion Time |
|-----------------|-----------------|-----------------|-----------------|
| Self-Transport  | EMS             | Difference      | Confidence Interval |
| Door to Troponin Time (DTT) | 4260 seconds (71 min) | 3000 seconds (50 mins) | 1260 seconds | 717.90, 1802.10 | <0.001 |
| Door to ECG Time (DTE) | 1577 seconds (26.28 min) | 1506 seconds (25.1 min) | 71 seconds | -135.02, 277.02 | 0.404 |
Does mode of arrival to the emergency department influence door-to-electrocardiogram or door-to-troponin times?

RESULTS

Of the 1000 patients included in the study, 648 arrived by self-transport and 352 of arrived via EMS. On average, the self-transport group was significantly younger (58.8 years versus 65.1 years; \(p<0.001\)) but the two groups were not significantly different in terms of sex (Tables 1 and 2). The self-transport group had a significantly longer median DTT time of 4260 seconds (71 minutes) than the group that arrived via EMS of 3000 seconds (50 minutes) \(p<0.001\), and the two groups had comparable DTE times (Table 3).

DISCUSSION

Minimizing door-to-ECG and door-to-troponin times is integral to decreasing the time it takes for patients with AMI to reach myocardium-saving interventions such as PCI. Importantly, this study revealed that the door-to-troponin collection time took significantly longer for patients who arrived by self-transport to the ED than for patients who arrived by EMS. Our study was not designed to determine if this 21-minute difference in DTT was clinical significant, and future studies should address this question. Although there was no significant difference in DTE times between the two modes of arrival, both were more than double the ten-minute DTE benchmark. These findings demonstrate that room for improvement exists in our two EDs to not only reduce DTT time for self-transport patients, but to reduce DTE and DTT times for all patients, regardless of mode of arrival. Since previous studies have shown that patients who arrive by EMS do not have a significantly higher rate of AMI compared with patients arriving via self-transport, equal urgency and consideration must be given to patients with chest pain, regardless of method of arrival11.

Evidence shows that simple, directed changes in the ED can change DTE and DTT times and ultimately, door to balloon times3,9,12,22. Other centres have shown that removing the registration and triage processes for chest pain presenters was shown to help increase the number of patients who met door to ECG benchmark times of less than ten minutes from 16% to 64% and subsequently increased the number of patients who met the door to balloon time goal of 90 minutes13,19. Similarly, moving an ECG machine and dedicated ECG technician to the walk-in triage area has reduced both DTE and door to balloon times3,10,12,22. A physician in triage has also been shown to reduce door-to-troponin times16. The same can be done for cTn draws, with the same ECG technician being responsible for drawing a cTn and sending it to the lab immediately. Along with this measure, a chief-complaint based “cardiac focused” triage system can be initiated23. In this system, patients who have chest pain bypass regular registration and triage, and go straight to a separate area, where an ECG and cTn blood draw are conducted immediately. This could be helpful for self-transport patients to minimize time spent triaging and registering patients that may not always be an issue for an EMS patient17,22.

An important first step in reducing the disparity in DTT times between EMS and self-transport patients would be identifying reasons why EMS patients had a shorter door to cTn time than self-transport patients. Possibilities include the fact that patients arriving by EMS might be seen in a separate, less busy triage area than self-transport patients, making it easier for cTns to be drawn right away; or because they have EMS personnel to advocate on their behalf and relay the seriousness of their condition. The data collected in this study can be used by our two Hamilton EDs to examine their assessment protocols for patients presenting with chest pain with cardiac features.

Limitations in this study include those inherent in any medical record review study23. All efforts were made to minimize those weaknesses, such as audits of data collection to ensure inter-rater reliability. The charts used for data collection were chosen from a large pool, and selection was completely random. However, since charts were reviewed and data entered manually, the potential for human error exists. Data abstractors were also not blinded to the outcome of the study. In this study, although benchmarks for DTT time refer to the time it takes to obtain results, DTT time was measured in terms of “collection time” rather than “result time”, since the authors did not have access to reliably recorded data that indicated when results of cTns were viewed. Additionally, we did not measure door-to-intervention time or record any patient outcomes - we believe that the examination of these metrics would be an excellent next step for future studies.

CONCLUSION

Patients who arrived at the ED via EMS had significantly lower door-to-troponin times than patients who arrived via self-transport. The two Hamilton EDs assessed in this study did not meet the recommended benchmark of ten-minute DTE time. These results can be used by these EDs to examine their approach to patients with chest pain and consider the implementation of strategies to reduce these times.

References

7. Cervellin, G. Chest pain and highly-sensitive troponin testing: The perspective


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Evaluating the role of physician mentorship among undergraduate medical students

ABSTRACT:

Background: Mentorship is a key factor for a successful academic medical career, earlier career choices, and increased research productivity. This study characterized the prevalence and medical student perception of physician-medical student mentorships. It also aimed to provide guidance for physicians on finding, mentoring and inspiring young medical minds.

Methods: A 23-question survey was sent electronically to medical students at McMaster University, Hamilton, Ontario. Questions examined the initiation, duration, and productivity of mentorship relationships, and the characteristics of mentors and mentees. Population data was collated and analyzed. Fill-in responses were manually tabulated.

Results: Of 629 medical students, 244 (38.7%) responded. Mentors were largely academic (63.89%) and in the students’ field of interest (53.85%). Mentored students exhibited no difference in years of education, age or intention to pursue specialty training, compared non-mentored students. Mentored students had more intent to pursue an academic practice (p<0.05), and less intent to pursue community practice (p<0.05). Research publications (13.33%), presentations (18.89%) and establishing connections in a field of interest (57.78%) were identified as productivity arising from mentorship.

Conclusion: Mentorship enhances career planning, research productivity and education. Mentored students express more intent in practicing academic medicine. Medical schools may benefit from programs that pair students with clinical mentors. Communication, respect, and genuine interest form the foundation for a good mentorship.
INTRODUCTION

Mentorship is recognized as a key factor in contributing to a successful career in medicine. A mentor is vital for facilitating career advancement, as well as acquisition of clinical and research skills. Career counseling by mentors leads to earlier career choices by junior trainees. Mentoring also increases the odds of participating in research during medical school and correlates with increased research productivity in junior academic physicians. The converse also appears to be true; lack of mentoring has been identified as a hinderance to career advancement in medicine due to the insight mentors provide into the career development process for mentees.

Despite the research consensus surrounding the benefit of medical mentorship, formal clinical and research mentorship programs remain elusive among Canadian undergraduate medical programs. Cross-sectional studies reveal that only a limited number of medical students are enrolled in formal mentoring programs and only a fraction of those receive one-on-one mentoring. The research on medical mentorship is limited in that much of it does not use standardized, validated questionnaires investigating the effects of student mentoring. There is also confusion in the literature surrounding the difference between an advisor, role model, and career mentor. These research limitations have made it difficult to understand which characteristics of mentoring relationships effect undergraduate productivity, specialty selection, and career trajectory.

The goal of this study is to determine how mentorship relationships are developed among undergraduate medical students and senior staff at McMaster University and how students perceived their mentorship relationships. Using the data collected, we attempted to characterize the tools required to foster a good mentoring relationship.

METHODS

After an extensive literature review and evaluation of current mentorship program at McMaster University, we designed a 23-question survey for data collection. The survey and research protocol were discussed with the Research Ethics Board (REB) at McMaster University and determined to meet criteria for a quality improvement study, and therefore did not require a detailed REB review. The survey was distributed electronically to all medical students at the Michael G. DeGroote School of Medicine in Hamilton, Ontario, Canada. There were no specific demographic inclusion or exclusion criteria for participants, all medical students currently enrolled were eligible to participate. A single reminder was sent to all students to encourage participation. The survey was designed by the authors (LM and JLM) with input and feedback from the School of Medicine Student Advisor program. As there were no similar studies located during our literature search, our survey was not based on previously published work and was not validated. A copy of our survey is provided in Appendix 1.

Data collected included student mentee demographics including age, gender, highest level of education obtained, and CaRMS match result (optional) as well as career goals, mentor demographics, mentor-mentee interaction characteristics and perceived positive and negative mentor relationship traits. Individual student identifiers were not collected to protect participant confidentiality.

For quantitative data analysis, Medcalc statistical software (https://www.medcalc.org/) was used to assess differences in proportions of responses between students with mentors and those without, as well as within the group of students with mentors. Data were compared using a z-test for population proportions. For all population differences, a two-sided p-value of 0.05 was used. Fill-in responses were manually tabulated with two authors (JLM and LM) assigning themes to responses. Themes were collated and presented with analysis.

RESULTS

239 students of a possible 629 undergraduate medical students completed the survey, yielding a response rate of 38.0%. Third-year students comprised 36.4% (n = 87) of responses; second-year students comprised 26.6% (n = 65) of responses and first year students made up 36.4% (n = 87) of responses. Most students’ highest level of education was an honours bachelor degree (56.15%, n = 137), while 17.62% (n = 43) had a post-graduate degree (masters or PhD). The majority of students were aged 22-24 (56.15%, n = 137).

Almost half the students had a mentor (44.77%, n = 107). Of the 132 respondents who did not have a mentor, 57 (43.18%) noted not having a program or opportunity to connect with mentors in their field of interest. Mentors were largely academic (63.89%, n = 69) physicians, who were established (5-15 years of practice, 36.45%, n = 39) or experienced (15+ years of practice, 49.53%, n = 53) clinicians. More than half (53.85%, n = 56) the mentors were physicians in the students’ field of interest and were based out of the students’ home medical school (78.30%, n = 83). There was no proportionate difference in undergraduate year, age, or highest degree obtained, between students with a mentor and those without (Table 1). The proportion of students with a mentor was not significantly different between students pursuing family medicine (35% n = 14 vs. 40% n = 16, p = 0.174) or specialty training (65% (n = 26) vs. 60% (n = 24), p = 0.509). However, students with a mentor did intend to practice as an academic physician more frequently than those without, and had less intent to practice as a community physician (Table 1). First year students were more likely to be uncertain of future residency training choice compared to second year students (85.51% n = 59 vs. 14.49% n = 10, p <0.05), and conversely second year students were more likely to be certain of future residency training choice compared to first year students (65.91% (n = 58) vs. 34.09% (n = 30), p < 0.001).

Mentorship relationships were mostly started as part of a formal program or a clinical rotation (52.83% (n = 56) and 18.87% (n = 20), respectively). Contact usually occurred less than once a month (54.21%, n = 58), primarily through email (64.49%, n = 69) and in-person meetings (23.36%, n = 25). Popular topics of discussion...
Evaluating the role of physician mentorship among undergraduate medical students

Table 1. Comparison of baseline characteristics, future training and practice intentions between students with and without a mentor. Note, not all responders answered all questions, as a result, the total number may be larger than the number in each section.

<table>
<thead>
<tr>
<th>Year of Study</th>
<th>Total</th>
<th>Have Mentor</th>
<th>Sample Size</th>
<th>No Mentor</th>
<th>Sample Size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st year</td>
<td>87</td>
<td>38.32%</td>
<td>41</td>
<td>34.85%</td>
<td>46</td>
<td>0.582</td>
</tr>
<tr>
<td>2nd year</td>
<td>65</td>
<td>27.10%</td>
<td>29</td>
<td>27.27%</td>
<td>36</td>
<td>0.976</td>
</tr>
<tr>
<td>3rd year</td>
<td>87</td>
<td>34.58%</td>
<td>37</td>
<td>37.88%</td>
<td>50</td>
<td>0.596</td>
</tr>
<tr>
<td>Highest Degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No undergraduate degree</td>
<td>15</td>
<td>5.61%</td>
<td>6</td>
<td>6.06%</td>
<td>8</td>
<td>0.881</td>
</tr>
<tr>
<td>Non-Honours Undergraduate</td>
<td>43</td>
<td>20.56%</td>
<td>22</td>
<td>15.91%</td>
<td>21</td>
<td>0.352</td>
</tr>
<tr>
<td>Honours Undergraduate</td>
<td>136</td>
<td>53.27%</td>
<td>57</td>
<td>59.85%</td>
<td>79</td>
<td>0.308</td>
</tr>
<tr>
<td>Masters</td>
<td>39</td>
<td>16.82%</td>
<td>18</td>
<td>14.39%</td>
<td>19</td>
<td>0.603</td>
</tr>
<tr>
<td>PhD</td>
<td>4</td>
<td>0.93%</td>
<td>1</td>
<td>1.52%</td>
<td>2</td>
<td>0.689</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-21</td>
<td>20</td>
<td>10.28%</td>
<td>11</td>
<td>6.82%</td>
<td>9</td>
<td>0.337</td>
</tr>
<tr>
<td>22-24</td>
<td>136</td>
<td>55.14%</td>
<td>59</td>
<td>58.33%</td>
<td>77</td>
<td>0.617</td>
</tr>
<tr>
<td>25-27</td>
<td>54</td>
<td>26.17%</td>
<td>28</td>
<td>19.70%</td>
<td>26</td>
<td>0.234</td>
</tr>
<tr>
<td>28+</td>
<td>29</td>
<td>8.41%</td>
<td>9</td>
<td>15.15%</td>
<td>20</td>
<td>0.111</td>
</tr>
<tr>
<td>Proposed Residency Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Medicine</td>
<td>30</td>
<td>35%</td>
<td>14</td>
<td>40%</td>
<td>16</td>
<td>0.174</td>
</tr>
<tr>
<td>Specialty</td>
<td>50</td>
<td>65%</td>
<td>26</td>
<td>60%</td>
<td>24</td>
<td>0.509</td>
</tr>
<tr>
<td>Future Practice Intentions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic Physician</td>
<td>237</td>
<td>3.62</td>
<td>105</td>
<td>3.02</td>
<td>132</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Community Physician</td>
<td>237</td>
<td>3.85</td>
<td>105</td>
<td>4.20</td>
<td>132</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Private Industry</td>
<td>237</td>
<td>2.03</td>
<td>105</td>
<td>2.01</td>
<td>132</td>
<td>0.987</td>
</tr>
<tr>
<td>International Medicine</td>
<td>237</td>
<td>2.63</td>
<td>105</td>
<td>2.52</td>
<td>132</td>
<td>0.099</td>
</tr>
<tr>
<td>Consultant</td>
<td>237</td>
<td>2.69%</td>
<td>105</td>
<td>3.00%</td>
<td>132</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

DISCUSSION

The topic of mentorship among medical students has proven difficult to study, as both the concept of mentorship and its desirable outcomes can be vague, difficult to define, and challenging to assess. However, the benefits of mentorship have been documented in detail, and include career counseling, guidance in research, and clinical skills development. For our study, a mentor was defined as a role model who guides students in the development and re-examination of their own ideas, learning, and personal and professional development. Our study aimed to determine how mentorship relationships developed, how students perceived their mentorship relationships, whether they resulted in increased clinical and research productivity, and how to foster a good mentoring relationship.

**What does it mean to have a formal mentor?**

Medical students will interact with many clinical and non-clinical faculty throughout their medical education both within and outside of structured teaching environments. These interactions may lead to connections or further work with specific individuals. However, the mentor-mentee relationship is unique and is not defined only by the frequency, duration and type of interactions between individuals. The survey administered did not offer a specific definition of “formal mentor” in order to encourage responders to utilize their own perspectives and understanding of the mentorship process. A common response by participants who reported not having a formal mentor was that they have clinicians whom they consider informal...
mentors or who they interact with on a frequent basis outside of their structured clinical teaching environment, but do not consider these individuals to be their formal mentors. The survey administered does not delve further into this, however, this response suggests that implementation of a curriculum component centered on the needs of medical students and the roles that mentors can assume may help students more readily identify opportunities for mentorship and maximize these interactions.

Are students who have mentors different from those that don’t? What are the benefits of a mentor?

This study showed that at McMaster University, medical students were almost as equally likely to find a mentor throughout their undergraduate training as they were to finish the program without a formal mentor. There were no demographic differences (age, education, intended residency choice) between students who had mentors and who did not, which is consistent with other studies. Students who had mentors showed greater interest in practicing academic medicine in the future, and less interest in working in the community. Additionally, many students reported completing research with their mentor, and approximately half of those students produced a peer-reviewed publication during their undergraduate medical training. At McMaster’s medical school, there is currently no formal mentorship program, however, students are provided with a student advisor, a faculty physician who works with students to promote career planning, and to assist with transitioning both into medical school and into clerkship. As this faculty member is assigned to the student, students often find themselves paired with an advisor who is not a clinician in their primary field of interest, does not have shared interests with the student, or may be unable to provide insight into the student’s desired clinical career path. Faculty advisors have an administrative responsibility towards ensuring students achieve academic success throughout the medical program, and have opportunities to engage in mentorship; however, engaging in mentorship is not a requirement for the position and varies from advisor to advisor.

As McMaster is a three-year medical program, students begin the process of their CaRMS applications earlier than at four and five-year medical

<table>
<thead>
<tr>
<th>Mentor Practice Type</th>
<th>Sample Size</th>
<th>What have you completed with your mentor (select all that apply)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic Physician</td>
<td>64.76%</td>
<td>Research</td>
<td>27.06%</td>
</tr>
<tr>
<td>Community Physician</td>
<td>28.57%</td>
<td>Clinical Elective</td>
<td>38.82%</td>
</tr>
<tr>
<td>Private Industry</td>
<td>0%</td>
<td>Horizontal Elective (Shadowing)</td>
<td>37.65%</td>
</tr>
<tr>
<td>International Medicine</td>
<td>0.95%</td>
<td>Tutorial</td>
<td>9.41%</td>
</tr>
<tr>
<td>Consultant</td>
<td>0.95%</td>
<td>Conference/Seminar</td>
<td>16.47%</td>
</tr>
<tr>
<td>Other</td>
<td>4.76%</td>
<td>Nothing</td>
<td>30.59%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mentor Career Stage</th>
<th>Sample Size</th>
<th>How would you rate your mentoring relationship?</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Staff (&lt;5 years)</td>
<td>10.48%</td>
<td>Poor</td>
</tr>
<tr>
<td>Established Clinician (5-15 years)</td>
<td>36.19%</td>
<td>Fair</td>
</tr>
<tr>
<td>Experienced Clinician (15+ years)</td>
<td>49.52%</td>
<td>Good</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is your mentor in the same field you intend to pursue?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mentor a Faculty Member at Home School</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How did you meet your mentor?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclerkship Tutor</td>
</tr>
<tr>
<td>Clinical Supervisor</td>
</tr>
<tr>
<td>Research Supervisor</td>
</tr>
<tr>
<td>Previous Connection</td>
</tr>
<tr>
<td>Student Advisor Program</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How often to you contact your mentor?</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than once a week</td>
</tr>
<tr>
<td>Once a week</td>
</tr>
<tr>
<td>Once a month</td>
</tr>
<tr>
<td>Less than once a month</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Mode of Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Person</td>
</tr>
<tr>
<td>Email</td>
</tr>
<tr>
<td>Phone</td>
</tr>
<tr>
<td>Texting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topics of Discussion (select all that apply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Clinical Electives</td>
</tr>
<tr>
<td>Clinical Skills/Knowledge</td>
</tr>
<tr>
<td>Research Advice or Guidance</td>
</tr>
<tr>
<td>Self-Care</td>
</tr>
<tr>
<td>Career Planning</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of mentorship relationships and productivity among medical students.
Evaluating the role of physician mentorship among undergraduate medical students

What benefits are associated with being a mentor?

Mentorship provides many benefits to the mentor, including both academic credit and teaching responsibilities. It also provides the opportunity to guide young physicians in their journey to becoming independent clinicians, fosters friendships among students and faculty, and allows for networking with future residents and eventually colleagues. With the increased emphasis on communication in medicine, the development of strong mentorship relationships provides both clinical and non-clinical faculty with the opportunity to develop a stronger understanding of the concerns, thoughts, and context of medical students in their transition to becoming clinicians. This knowledge may improve the quality of interactions with younger faculty both within and outside of their department. More objectively, it provides human capital for improving the academic environment at an institution, through medical education opportunities and research productivity.

How do interested clinicians find a mentee/mentor?

While some schools such as McMaster assign formal student advisors to students, it appears that students value mentors who are clinicians in their primary field of interest and maintain a clinical practice similar to the student’s planned career path. The student advisor program at McMaster serves an important role by providing students with a faculty advisor who is engaged in their learning and able to offer insight into the medical school evaluation process, the development of a preliminary plan for career exploration and a better understanding of some of the day-to-day responsibilities of a clinician. When setting up formal mentorship programs, our study suggests students would benefit more from broad exposure to clinicians from a variety of clinical fields with a diversity of career focuses ranging from academic and community clinicians to administrative physicians. For clinicians, finding a student to mentor will primarily come from research opportunities and clinical electives. As students complete research projects or clinical rotations, taking the time to get to know them and provide advice is a good way to transition from being a supervisor to a mentor. Students are encouraged to initiate conversation by requesting meetings with their mentor. Working with a clinician is the best way to start a mentorship, as this promotes organic discussion (compared to a formal program) and allows for longitudinal communication.

Are program-implemented formal mentorship programs useful?

A formal mentorship program could serve as a meeting point for medical students with interested faculty members. Within McMaster’s medical school, this study identified a trend toward more senior students having a greater sense of which field of medicine they wanted to pursue; however only 34.09% of first year students wanted to pursue a specific residency training program. As a result, the implementation of formal mentorship programs is best suited to second, third and fourth year students. For first year medical students, programs allowing early clinical exposure to different patients, practice settings and potential clinician mentors may help students understand the scope of medicine, as well as put their classroom education into a clinical context. The survey results show significant variability in the types of communication utilized by mentors and mentees, the frequency of this communication, and the expected goals of the mentorship relationship. This diversity in experience makes the development of a structured formal mentorship program significantly more difficult and may not appeal to the majority of students or mentors. The survey results do suggest that a formal mentorship program which assists both students and mentors in understanding the role of a strong mentorship relationship and introduces medical students to interested mentors would significantly benefit students interested in developing mentorship relationships who have not yet had the opportunity to do so through their personal networking and experiences.

What makes for a good mentor?

Students in our study mentioned many traits that a good mentor embodied (Table 3). Communication was almost always mentioned, and in our opinion, is the foundation of a good mentorship. When starting a mentorship relationship, a discussion about the frequency and mode of communication to be utilized will be helpful for both mentors and mentees. Students may often feel like they are bothering their mentor by emailing them or visiting them while completing clinical rotations, especially early in the relationship. By establishing frequency of communication early, mentors can touch base with their students regularly, and students can communicate with their mentors without feeling like they are imposing or extending beyond the boundaries defined.

Table 3. Qualities medical students find beneficial or detrimental to a mentorship.

<table>
<thead>
<tr>
<th>Qualities of a Good Mentor</th>
<th>Qualities of a Poor Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication (n = 32)</td>
<td>Lack of communication (n = 23)</td>
</tr>
<tr>
<td>Respect (n = 13)</td>
<td>Unreliable (n = 6)</td>
</tr>
<tr>
<td>Approachability (n = 14)</td>
<td>Lack of Commitment (n = 8)</td>
</tr>
<tr>
<td>Reliability (n = 7)</td>
<td>Lack of Interest (n = 5)</td>
</tr>
<tr>
<td>Similar Interests (n = 19)</td>
<td>Biased when Giving Career Advice (n = 4)</td>
</tr>
<tr>
<td>Knowledgeable (n = 5)</td>
<td>Lack of Respect (n = 6)</td>
</tr>
<tr>
<td>Genuine Interest in Students (n = 4)</td>
<td>Descending (n = 3)</td>
</tr>
</tbody>
</table>

https://mdprogram.mcmaster.ca/md-program-research/recognizing-student-research/mumj
Strengths and Limitations

As with any survey, the findings we present in this article are limited by selection bias of responders and medical students who would be more likely to participate in an optional survey. Additionally, these findings come from a cross-sectional sample, and as such cannot imply any causation between variables. Our study was limited to medical students’ perspectives and would benefit from involvement of mentors and their perspectives. However, this study does effectively catalogue the distribution, productivity, and characteristics of mentor-mentee relationships at a 3-year medical school. The results encompassed students from every year of medical school, and as a result, were able to study how mentorship relationships are formed and what students found beneficial or detrimental to establishing and maintaining these relationships. As medical education trends to more condensed undergraduate education, and increasing sub-specialization in postgraduate training, determining the contributions of mentorship in residency selection and practice setting should help guide curriculum development and residency education for years to come.

CONCLUSION

Mentorship is a useful tool for career planning, research development, and clinical education opportunities. Students with mentors were able to meet physicians in their fields of interest, produce research manuscripts and present at conferences. Mentors offered insights into many aspects of physician life varying from self-care to planning for electives. Medical schools may benefit from starting formal programs that pair students with clinicians in their field of interest. The implementation of formal programs should be targeted towards intermediate and upper year students and focus on developing opportunities for interactions between potential mentors and medical students. Communication, respect, and a genuine interest in student mentorship form the foundation for a good mentorship. Future avenues for research include quantitatively examining the research productivity of students with mentors, comparing formal vs. informal mentors, and determining the degree of clinical education that occurs as the result of mentorships.

References

Longitudinal civic-mindedness in siblings of Ontario children with chronic illness

ABSTRACT:

Introduction: The purpose of this study was to examine longitudinal associations between being a sibling of a child with chronic illness and civic-mindedness in adulthood.

Methods: Secondary data analysis was conducted using data from the Ontario Child Health Study (OCHS) in 1983 and 2000. Multiple linear regression was used to examine adult civic-mindedness in healthy siblings of children with and without chronic illness (N = 1,051).

Results: For healthy siblings, adult civic-mindedness was significantly associated with the age (older), higher family socioeconomic status (SES), being a good student and participating in extra-curricular activities. There was a positive association between family SES and adult civic-mindedness for siblings of healthy children, but this relationship was weaker for the siblings of children with chronic illness. SES significantly moderated the interaction between sibling status and adult civic-mindedness for siblings of healthy children (p < .001), but not for siblings of children with chronic illness.

Conclusion: Research supports that certain advantages in childhood, including socioeconomic advantage, are related to civic-mindedness as an adult. Siblings of children with chronic illness may develop greater social maturity than healthy siblings of healthy children in low SES households, effectively making these children equally civic-minded in adulthood as siblings who come from high-SES households.
INTRODUCTION

A diagnosis of paediatric chronic illness (a health condition lasting for years or even the entire lifespan) can be quite devastating for families and may enhance tension within the family unit, especially if other siblings are involved in the rearing of the child. Siblings of chronically ill children may experience recurrent interruptions in their daily activities and the needs of the ill child are often prioritized. Siblings face many challenges, including processing the shift in parental attention towards the child with the chronic illness and contending with subsequent feelings of abandonment, navigating the complicated workings of sibling relationships, and negotiating feelings of jealousy and guilt about perceived preferential attention towards the ill child. A study on services provided to siblings of children with chronic illness found that siblings experienced hyper-responsiveness to changes in routines, separation anxiety towards parents, and felt confused and displaced from formal family order. Siblings of children with chronic illnesses can react with stress (e.g., feelings of responsibility, jealousy, fear, guilt, loneliness, resentment, sadness and embarrassment). Other research has found that siblings of children with chronic illness are at an increased risk of psychosocial distress, emotional disorder and poor peer relations, depression, anxiety and social isolation, internalizing and externalizing behaviour problems, lower self-esteem, and poorer academic performance.

Because siblings of children with chronic illness might have early adverse childhood experiences, it is important to know how these experiences might affect their longitudinal psychosocial health outcomes when they become adults. Furthermore, there is a dearth of research on the psychosocial effects of paediatric chronic illness that uses both longitudinal data and population-based samples for analysis. Understanding the longitudinal relationship between paediatric chronic illness and psychosocial outcomes in adulthood is important in order to identify factors that mitigate risks that siblings of children with chronic illness might face.

While the vast majority of the literature in this area report negative outcomes, a small number of studies report no significant difference between siblings and their healthy counterparts in terms of social competence and adjustment and school performance. Still, most of these studies are cross-sectional and use small, clinic-based samples as sources for the data. It is also important to note that the literature on healthy siblings of children with chronic illness also reports some positive effects, in addition to the negative psychosocial effects. Some studies have found that siblings experience positive psychosocial effects including enhanced family intimacy, good sibling relations, personal growth and social maturity. These positive outcomes might point to some resilience in this population.

After examining literature on positive psychosocial development and considering the findings in the context of paediatric chronic illness and family systems, it was hypothesized that healthy siblings of children with chronic illnesses could exhibit more adult civic-mindedness than healthy siblings of healthy children because, being responsible for and attentive to a brother or sister with chronic illness, may provide more opportunities to develop compassion, empathy and social maturity through caring-for and learning to understand the lived experience of their sibling with chronic illness.

Additionally, the inconsistency in the literature may represent a failure to properly account for family attitudes and resources. Family characteristics, like SES, may be a factor that affects these risks to healthy siblings of children with chronic illness. SES could be associated with a set of attitudes and expectancies, which help determine how children fare when faced with adversity. For instance, family cohesion, consistency, values, and orderliness have all been thought to moderate the relationship between SES and child resilience. Therefore, we found it important to include SES as a possible moderator of the relationship between being a sibling of a child with chronic illness and positive psychosocial health outcomes in adulthood.

Objective

The objective of this study was to use longitudinal data from the Ontario Child Health Study (OCHS) to investigate the relationship between paediatric chronic illness and a positive psychosocial outcome, conceptualized as civic-mindedness, in healthy siblings. Specifically, we looked at whether these siblings were more likely to exhibit greater levels of civic-mindedness in adulthood than healthy siblings of healthy children and how the relationship might be moderated by family SES.

Theoretical Foundations

Family Systems Theory

Children with chronic illness and their siblings grow up in many environmental contexts, including the familial environment. According to Bowen’s Family Systems Theory, the family is a social system, influencing the functioning of every family member. According to Bowen, a change in one person’s functioning can lead to changes in the functioning of others.

Paediatric chronic illness changes the system, structure and function of the family unit. The illness often becomes the organizing principle of family life, such that the family may sacrifice other priorities in an attempt to cope with changes brought on by the illness. According to Cohen, childhood chronic illness imposes severe stresses called "generalized impact of illness stresses." Families coping with these illness stressors are more likely to develop dysfunctional family patterns and the physical, mental, social and emotional demands of chronic illness on family members exacerbate these negative effects.

Illness...
related stresses could restructure the roles of family members, as well as shift relationships between parents and siblings\(^\text{31}\). Constant exposure to health care personnel, teachers, and social workers may invoke the "uniquely intimate landscape" of the family\(^\text{31}\). Furthermore, patterns in family functioning may change as a result of stresses on the family structure\(^\text{31}\). Families often adopt certain roles and strategies to help them preserve normalcy and a sense of control\(^\text{39}\).

Using this Family Systems framework\(^\text{30}\), chronic illness could be an "infectious agent" within a family and, therefore, could be traumatic or compromise the integrity of the relationships in the family unit. The illness experience can produce incrementally traumatizing experiences, not only for the individual with the illness, but also for other family members\(^\text{31}\). However, not every traumatized individual will develop trauma symptoms\(^\text{35}\). In fact, some traumatized children are resilient and capable of thriving despite being exposed to severe stressors\(^\text{34}\). If family units are resilient and, as such, may cope with childhood chronic illness, then the healthy sibling may benefit from the exposure to this positive coping. This is perhaps why the relationship between being a healthy sibling of a child with chronic illness and adult civic-mindedness may vary as a function of family processes and attitude variables indicative of strength or weakness (e.g., SES).

**Positive Development**

"Post-traumatic growth" refers to the positive psychological change that may result from dealing with stress or challenging life circumstances\(^\text{35}\) – a traumatized person may function at a higher level than before\(^\text{36}\). The degree of post-traumatic growth is a function of many factors, including the severity of the traumatic event(s), the traumatized individual's optimism and self-concept, the effectiveness of that individual's coping mechanisms, and the availability of social support\(^\text{37}\).

There are factors that may distinguish all "resilient" children from others. Involvement in extracurricular activities may foster and display individual talents, thereby contributing to an individual's global sense of competence, esteem, efficacy and wellbeing\(^\text{38}\). These extracurricular activities may also promote the child's involvement in social networks, which could then promote achievement or socially appropriate conduct\(^\text{38}\). Additionally, many cross-cultural studies have found that opportunities for participation in socially or economically useful tasks are related to heightened self-esteem, enhanced moral development, increased political activism and the ability to create and maintain complex social relationships\(^\text{39}\). Healthy siblings may also be caretakers of their brothers or sisters with chronic illness. While adopting the role of the "caretaker" may cause psychosocial distress or burden, it may also allow for the healthy sibling to engage in activities that promote development of social maturity, empathy, and altruism – behaviours that may be considered to be reflected in the civic-mindedness measure utilized in this study (donating to charity, volunteering with a formal organization, volunteering informally, donating blood, and being part of a religious group or community organization).

**Current Study**

This study aimed to examine the longitudinal effects of pediatric chronic illness on healthy siblings. If chronic illness is considered to be a traumatic event, then, according to research on positive psychosocial development, healthy siblings of children with chronic illness may have more positive outcomes than healthy siblings of healthy children because having a sibling with a chronic illness may allow for opportunities to develop skills in social maturity, empathy and altruism\(^\text{31,32,40-43}\). Additionally, the mixed results in the literature about the effects of pediatric chronic illness on healthy siblings could be due to omission of the family context. Therefore, SES was tested as a moderator of the association between being a healthy sibling of a child with chronic illness and adult civic-mindedness.

**METHODS**

**Data Collection**

This study examined data from the Ontario Child Health Study (OCHS), a prospective epidemiological study that was the collaborative work of Statistics Canada and McMaster University. Investigators followed the same cohort of children over a 17-year period in order to track early childhood experience and longitudinal health outcomes\(^\text{45}\). Data were collected from 1,869 Ontario families with 3,294 children 4-16 years of age, and explored the factors that impact both pediatric health and subsequent functioning as an adult\(^\text{44,45}\). There were three periods of data collection: 1983, 1987 and 2000\(^\text{45}\).

In the first period of data collection (1983), information was obtained via home interview conducted by trained interviewers from Statistics Canada. In each household, the interview was conducted with a primary parent respondent, 95% of whom were mothers. Parental reports included both parental health and health of the children in the household. In the final follow-up period of data collection (2000), original respondents were located and interviewed, yielding a response rate of 71.5%. Detailed information regarding survey design and methodology of the OCHS can be obtained in Boyle et al\(^\text{44,46}\).

This study used data from all children aged 4-16 years who were eligible for the study in 1983. This cohort was between 21-33 years of age when participating in the final period of data collection, which started in 2000 and continued into 2001. Of the individuals who did not participate in 2001, 910 were non-respondents, 26 were excluded because of death and 3 were excluded because they were institutionalized\(^\text{44}\). Families were recruited for the study sample and the sample consists of two family groupings: one or more healthy siblings who have one or more brothers/sisters with a chronic illness,
as well as two or more siblings in families where no children have a chronic illness. This resulted in a final sample size of N = 1,051 healthy siblings in 2000 that were examined in this study.

**Variables and Measures**

**Dependent Variable**

The number of civic-minded activities (donating to charity, volunteering with a formal organization, volunteering informally, donating blood, and being part of a religious group or community organization) engaged-in in adulthood was the dependent variable.

**Independent Variables**

Chronic illness included blindness, visual problems (even with glasses), deafness or hearing problems (even with hearing aids), absence of speech or other severe speech problems, persistent pain, asthma, heart problems, epilepsy or convulsions without fever, kidney disease, arthritis, cerebral palsy or other paralysis, muscular dystrophy or other muscle diseases, spina bifida, diabetes, cancer, cystic fibrosis, missing limbs, physical deformities (missing extremities, limbs, cleft palate, club foot), and miscellaneous other health problems of comparable severity and chronicity.

Upon reviewing the literature on the psychosocial effects of chronic illness on healthy siblings, it was found that several variables – age and birth order, sex, academic achievement, family size, family dysfunction, and family socioeconomic status – are important predictors of both positive and negative sibling psychosocial adjustment. For this reason, demographic variables included the child’s age in 1983, child’s sex, and whether or not their household was in a small urban-rural area or an urban area. The child level variables were the child’s birth order, whether or not their teacher reported them to be a “good student” (yes/no), a scale-based measure of their emotional and behavioural functioning (derived from 13 source variables), whether or not parents endorsed them having “good friendships” (yes/no), the number of activities the child had participated in over the past year (e.g., sports involving coaching or instruction, music lessons, dance, art, other non-sports activities or membership in a club or group with adult leadership) and a parent report of how well the child got along with family, peers, and teachers in the past six months. Family-level variables include a measure of family SES, a measure of family dysfunction (derived from 12-item McMaster Family Assessment Device), and the number of people in the household.

**Statistical Analyses**

**Preliminary Analyses**

Descriptive statistics (means and standard deviations) were generated for each variable used in the analyses. The variables in the analyses were examined for the assumptions of multivariable analysis. The dependent variable, civic mindedness, was cross-tabulated with independent variables to ensure there were no empty cells. Descriptive statistics were run to examine skewness and kurtosis. To further test for normality, Kolmogorov-Smirnov and Shapiro-Wilk tests were completed. All analyses were conducted using SPSS.

Multicollinearity was examined using Pearson, Point-biserial and chi-square analyses. The continuous variables were centered using group mean centering taking each score and subtracting the mean of the scores for that variable. Centering data on the mean helps minimize multicollinearity.

**Sample Characteristics and Group Differences**

Chi-square tests and one-way Analysis of Variance (ANOVA) were used to examine differences between healthy siblings of children with and without chronic illness on child and family-level variables, as well as the civic-mindedness variable.

**Multivariate Analysis**

A blocked multiple linear regression was used to predict number of civic-minded activities engaged-in in adulthood. The first block of predictors included child demographic variables: age, sex, and urban-rural. The second block included whether or not the healthy sibling has a chronically ill sibling. The third block included family variables: birth order, family dysfunction and family SES. Block four included child psychosocial variables: good student, emotional problems, good friendships, participation in extra-curricular activities and getting along well with others. Finally, block five included the interaction between being a sibling of a child with chronic illness and family SES.

**Post-Hoc Regression**

A post-hoc regression was done to explore the interaction between being a sibling of a child with chronic illness and family SES and the number of civic-minded activities engaged-in in adulthood in more detail. The sibling illness variable (e.g., whether the healthy child had a sibling with chronic illness), family SES, and the interaction were entered into a linear regression to obtain the regression coefficients for each variable.

**RESULTS**

**Preliminary Analyses**

**Sample Characteristics and Group Differences**

The characteristics of the sample are described in Table 1. Of the 2,026 healthy siblings included in the original 1983 sample, 82.9% (N = 1,680) were siblings of healthy children and 17.1% (N = 346) were siblings of children with chronic illness. In 1983, the mean age of siblings of healthy children was 10.11 (SD = 3.46), and 9.99 (SD = 3.55) for siblings of children with chronic illness. In this study,
## Table 1. Sample Characteristics and Group Differences for Healthy Siblings (N = 2,026)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Sibling of Child with Chronic Illness</th>
<th>Healthy Sibling of Healthy Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Children [n]</td>
<td>17.1 [346]</td>
<td>82.9 [1,680]</td>
</tr>
<tr>
<td>% Sex [female] [n] **</td>
<td>52.9 [183]</td>
<td>49.5 [831]</td>
</tr>
<tr>
<td>% Urban-Rural [small] [n]</td>
<td>43.10 [149]</td>
<td>39.30 [661]</td>
</tr>
<tr>
<td>Birth Order M, [SD] **</td>
<td>1.93 [0.88]</td>
<td>1.77 [0.80]</td>
</tr>
<tr>
<td>% Good Student [yes] [n] ***</td>
<td>55.90 [170]</td>
<td>59.40 [891]</td>
</tr>
<tr>
<td>Emotional Problems M, [SD] ***</td>
<td>3.11 [3.02]</td>
<td>2.68 [2.70]</td>
</tr>
<tr>
<td>% Good Friendships [yes] [n]</td>
<td>77.00 [264]</td>
<td>78.10 [1,292]</td>
</tr>
<tr>
<td>Getting Along Scale M, [SD] *</td>
<td>5.01 [1.73]</td>
<td>4.75 [1.81]</td>
</tr>
<tr>
<td>Participation Index M, [SD]</td>
<td>1.86 [1.67]</td>
<td>1.80 [1.69]</td>
</tr>
<tr>
<td>Families</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family SES M [SD]</td>
<td>0.31 [3.76]</td>
<td>0.29 [3.77]</td>
</tr>
<tr>
<td>Outcome Variables in 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Civic-Minded Activities M, [SD]</td>
<td>2.49 [1.29]</td>
<td>2.53 [1.29]</td>
</tr>
</tbody>
</table>

Chi-square tests were used to compare group differences between categorical variables, One-way ANOVA tests were used to compare group differences between continuous and categorical variables.

* p < 0.05; ** p < 0.01; *** p < 0.001.
† p < 0.10.

n = frequency within sample, M = mean, SD = standard deviation.
Detail may not add because of rounding.

Compared to siblings of healthy children, siblings of children with chronic illness were more likely to be females who were younger than their afflicted sibling. They were also more likely to not be classified as a “good student” by their teacher, have more emotional problems, get along with others, and be from families with higher dysfunction.

### Multivariate Analysis

Results of the linear regression are presented in Table 2. Of the child demographic variables (age, female, small urban-rural), only age was significantly positively associated with number of civic-minded activities engaged-in in adulthood. The illness variable (being a sibling of a child with chronic illness) was not significant. Of the family-level variables (birth order, family dysfunction, and family SES), family SES was significantly positively associated with civic-mindedness and age remained significant. In the fourth block, older age, family SES, being a good student, and participation in extra-curricular activities were all significantly positively associated with the outcome of civic-mindedness. Finally, the interaction between being a sibling of a child with chronic illness and family SES was significantly associated with the outcome. Age, higher family SES, being a good student, and participation in extra-curricular activities all remained significantly associated with the outcome in the final model. Model fit statistics for blocks one, three, four, and five indicate significant improvement to the previous models (see Table 2).

### Post-Hoc Regression

The regression equations for healthy siblings of children with chronic illness and healthy siblings of healthy children were graphed using the minimum and maximum values for SES (see Figure 1). The bar chart depicts an SES continuum, arbitrarily identified, in which the relationship between sibling status and civic-mindedness is portrayed. In the low SES condition, healthy siblings of children with chronic illness engaged in slightly more civic-minded activities (n = 2.62) than healthy siblings of healthy children (n = 2.60) (Figure 1). Simple slopes analysis revealed that the slope of the regression equation for healthy sibling of healthy children differed significantly from zero (p < .001), whereas the chronic illness healthy sibling status did not.

### DISCUSSION

For all healthy siblings, civic-mindedness in adulthood was significantly associated with older age, higher family SES, being a good student and participation in extra-curricular activities. These results are consistent with much of the existing research literature on the development of prosocial behaviour in adulthood. As hypothesized, there was a positive association between the interaction variables (SES and sibling status) and adult civic-mindedness. To further tease this relationship apart, we performed a simple slopes analysis.

Simple slopes analysis revealed that family SES significantly moderated the relationship between being a sibling of a healthy child and adult civic-mindedness (p < .001), making it stronger; however, it did not significantly moderate the relationship between being a sibling of a child with chronic illness and adult civic-mindedness, leading us to believe that the strength of the relationship between being a sibling of a child with chronic illness and being civic-minded...
in adulthood is independent of the family’s SES. Therefore, if the family had a low SES, this would make the siblings no less likely to be less civic-minded in adulthood than if the family had a high SES. This result is interesting when we consider it in relation to the hypothesis that healthy siblings of children with chronic illness would be more civic-minded in adulthood because they may have more opportunities to develop skills in compassion, empathy and social maturity (as a result of caring for or living with a brother or sister with chronic illness). It could be that having a sibling with a chronic illness denotes some protective effect against the influence of family SES on civic-mindedness.

In some of the literature on chronic illness and healthy siblings, these siblings have been found to experience positive effects\(^{40,41}\), including enhanced family intimacy\(^{42}\), good sibling relations\(^{43}\), personal growth\(^{44}\) and social maturity\(^{45}\). In their experiences with the child with chronic illness, the healthy sibling may contribute responsibly to physical and emotional care\(^{46}\). In a qualitative study on siblings of children with diabetes, all of the siblings reported closer relationships with their chronically ill brother or sister\(^{47}\). The same study reported that many parents educate the healthy siblings about the child’s condition or acknowledge that the healthy sibling has been educated through their experiences in dealing with the sick child\(^{47}\). It could be that responsibility, contribution, close relationships and education surrounding a chronic illness create a certain awareness of the importance of being civic-minded in the healthy sibling, one that translates to prosocial behaviour in adulthood. These interactions with a brother or sister with a chronic illness may teach the child the value of empathy, patience and altruistic behaviour. Perhaps the combined effects of the adversity of socioeconomic disadvantage and chronic illness in the family leads to other factors not measured in this study, such as greater empathy, social consciousness and social maturity in siblings, which may in turn boost levels of adult civic-mindedness to levels comparable to those who grew up in households with no childhood chronic illness and socioeconomic advantages. It could also be that families with low SES have less “baggage” (e.g., lower disappointment or guilt) and treat their child with chronic illness more normally, thus reducing the impact on the family and, inherently, the healthy sibling.

**Age**

Older children were found to be more civic-minded in adulthood, perhaps because the civic-mindedness variable was measured by the number of civic-minded activities in which they engaged in adulthood and, if they were older at the time of the initial and final waves of data collection, they had more time to engage in these activities (e.g., donating to charity, volunteering with a formal organization, volunteering informally, donating blood, being part of a religious group or community organization). It is also possible that older individuals may be more mature or have more life experience (e.g., 33-year olds versus 21-year olds), which may translate into engaging in more civic-minded activities.

**Family SES**

There is evidence that children from families with low SES are less likely to be civic-minded, as measured by volunteerism\(^{48}\). Higher levels of positive development (e.g., social competence, life satisfaction, trust and tolerance of others, trust in authorities and institutions and civic engagement) in adulthood have been related to higher SES while growing up\(^{49}\). Children from families with high SES may not have to work as adolescents and young adults and, therefore, may have more time to volunteer. Children who are raised in families with higher SES have more access to, and are more likely to take advantage of, neighbourhood resources and may be more likely to participate in activities and relationships that are psychosocially beneficial\(^{50}\).

**Good Student**

Children who were considered “good students” by teachers (yes/no teacher report) engaged in more civic-minded activities in adulthood. While there are limitations to this definition (as conceptualized in the OCHS), and this measure might be quite subjective regarding the teacher’s opinion of the student, this result is consistent with other literature maintaining educational attainment is a predictor of adult volunteerism\(^{51}\). Similarly, better adjustment in school has been linked to higher levels of positive development in emerging adulthood\(^{52}\). Being a good student may facilitate this adjustment in that teachers may hold good students in higher regard; whereas, if a teacher thinks a child is a poor student, the student may be able to perceive that. These are called expectation effects, which are documented in literature on educational psychology\(^{53,54}\).

**Extra-curricular Participation**

Participation in extra-curricular activities during childhood was significantly associated with adult civic-mindedness. Extra-curricular activities included sports involving coaching or instruction, music lessons, dance, art, other non-sports activities or membership in a club or group with adult leadership. All of these activities involve some degree of social interaction. A recent longitudinal study found that social interaction is associated with higher level of civic activities in youth and continues into adulthood\(^{55}\). In high school, participation in these sorts of activities predicts greater likelihood of volunteering\(^{56}\) and voting\(^{57}\) later in life. The authors posit that certain activities that are not necessarily inherently “psychosocial” (e.g., arts or sports) could be microcosms of public life and, as such, give individuals opportunities to build social skills needed for civic engagement\(^{58}\). For instance, being part of a sports team may require a child to learn teamwork, reciprocity and the value of having a common goal. These skills could also be part of the social skills needed for civic engagement. People may donate money to charity or volunteer for an organization because they believe in the goal of the civic activity and understand that it requires teamwork to attain this goal.
Limitations of this Study

There are several study limitations that must be considered. One of the caveats of longitudinal study is attrition. People drop out of the study for various reasons and longitudinal data is lost. Also, low-base rates of certain chronic illnesses in the population make chronic illness difficult to capture. Interpretation of the results should note attrition and low sample size.

Second, the chronic illness variable was parent-report and not verified by an external source. There is limited agreement between parents and children in report data\(^6,67\). One study found that parents of children with chronic illness reported more sibling adjustment problems than did the siblings themselves\(^64\). Parents might self-diagnose their child or exaggerate their child’s symptoms. They also might misunderstand their child’s diagnosis and report something that is inaccurate.

CONCLUSION

The findings of this study indicate that, in this combined sample of healthy siblings, adult civic-mindedness is significantly associated with being older, being a good student, higher family SES and more participation in extra-curricular activities, which is consistent with research on predictors of civic-mindedness or prosocial behaviour in adulthood\(^39,50,58\).

There was a significant association between number of civic-minded activities engaged-in in adulthood and the interaction between being a sibling of a child with chronic illness and family SES. Living with a sibling with a chronic illness in a family with lower SES could lead to greater social maturity and consciousness in these siblings, which may enhance levels of adult civic-mindedness to levels comparable those who spent their formative years in more affluent households, without any paediatric chronic illness.

It is important that we further explore exactly why siblings of children with chronic illness seem to be less affected (when compared to siblings of healthy children) by the influence of family SES, when it comes to demonstrating civic-mindedness in adulthood. It will be important to broaden our research and find ways to elucidate whether or not these children, in fact, do have more opportunities to cultivate skills and practice in social maturity, empathy, responsibility and altruistic behaviour. This way, our research might be able to inform policies and practices within realms of child health and development, allowing us to find ways of nurturing children, helping them to realize their potential as functioning, contributing members of society.
References

Longitudinal civic-mindedness in siblings of Ontario children with chronic illness

Table 2. Linear Regression Predicting Adult Civic-Mindedness (Number of Civic-Minded Activities Engaged-In) in Healthy Sibling.

(N = 1,051) in 2001

<table>
<thead>
<tr>
<th>Child Demographic Variables</th>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
<th>Block 4</th>
<th>Block 5</th>
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<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>β</td>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td>Age</td>
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<td>0.01</td>
<td>0.11***</td>
<td>0.04</td>
<td>0.01</td>
</tr>
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<td>0.02</td>
<td>0.05</td>
<td>0.08</td>
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<td>0.08</td>
<td>0.01</td>
<td>0.03</td>
<td>0.08</td>
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<td>0.11</td>
<td>0.01</td>
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<td>0.11</td>
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<td>0.003</td>
<td>0.02</td>
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<td>-0.57†</td>
<td>-0.01</td>
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<td>Family SES</td>
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<td>0.01</td>
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<td>Good Student (Yes)</td>
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<td>0.07*</td>
<td>0.20</td>
<td>0.09</td>
</tr>
<tr>
<td>Emotional Problems</td>
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<td>-0.003</td>
<td>0.00</td>
<td>0.02</td>
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<td>Good Friendships (Yes)</td>
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<td>0.10</td>
<td>0.02</td>
<td>0.06</td>
<td>0.10</td>
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<tr>
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<td>0.03</td>
<td>0.07*</td>
<td>0.06*</td>
<td>0.03</td>
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<td>Getting Along With Others</td>
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<td>0.01</td>
<td>0.002</td>
<td>0.03</td>
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<tr>
<td>Interaction Term</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sibling of Chronic Illness x Family SES</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2</td>
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<td>0.01</td>
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<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>F for Change in R2 a</td>
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<td>0.11</td>
<td>6.99***</td>
<td>2.32*</td>
<td>9.9.31**</td>
</tr>
</tbody>
</table>

p<.05, **p <.01, ***p <.001  †p <.10, *  (N = 1,051) in 2001

Block 1 fit statistics indicate improvement to the null model and Block 3, 4 and 5 fit statistics indicate improvement to the previous model.
ABSTRACT:

Background: Trauma is one of the leading causes of pediatric disability and death in Canada. Mortality is lower in trauma centres where a trained trauma team exists, signifying the importance of having efficient trauma care. At McMaster Children’s Hospital’s hospital, a series of trauma simulations were conducted in attempt to improve patient care. The objective of this study was to review the participant evaluations of 10 simulation sessions and examine how feedback was used to resolve systems issues locally.

Methods: Serial pediatric trauma in situ simulations were performed at the MCH Emergency Department (ED), a level 2 trauma centre with multidisciplinary ad hoc teams, from 2011 to 2012 to improve the quality of trauma care. Evaluation forms were distributed to participants and observers of the simulated trauma, asking what was learned, liked, and what should be changed. The comments on the form were collated and analyzed. Changes to the system made in response to the evaluations were reviewed.

Results: Participants and observers completed a total of 119 evaluation forms voluntarily during 10 simulations [mean 12 per session, ranging 9 - 16]. Feedback was obtained with regard to trauma team dynamics, educational needs, and system issues. Changes made to the system in response to the feedback included but were not limited to: improved communication processes, documentation processes, nursing education, defining roles and responsibilities, the relocation and acquisition of equipment in the ER, reorganization of the trauma bay, and identifying smocks for team members.

Conclusion: Pediatric trauma in situ simulations are valuable in helping to identify and resolve system issues. They also provide an excellent opportunity for an “ad hoc” multidisciplinary team to rehearse trauma care and to promote continuous quality improvement.

BACKGROUND

Trauma is one of the leading causes of pediatric deaths. Approximately 200 children in Canada younger than 15 years of age die every year secondary to traumatic injuries, contributing to 20-30% of total deaths in this demographic. Mortality is lower in trauma centres where a trained trauma team exists, signifying the importance of having efficient trauma care. In response to this data, multidisciplinary simulation-based trauma training and other educational programs have been established to improve teamwork and the performance of trauma teams. Practice makes perfect, however, opportunities for practice are extremely limited in real life trauma settings. It is not surprising that patient safety often takes precedence over training for the learners present during acute trauma care.

The ability of simulation to offer education without patient-risk and demonstrate multiple medical scenarios makes it an integral part of medical education. Simulation training exists in multiple forms, including role-play, standardized patients, computer-based, video-based, and realistic interactive simulators. In particular, realistic

https://mdprogram.mcmaster.ca/md-program-research/recognizing-student-research/mumj
interactive simulators are suitable for trauma care training given their ability to teach and evaluate technical skills. In situ simulations, refers to simulations in real-life settings (i.e. MCH ED), have proven to be a useful method of training resuscitation skills and teamwork in multiple studies. However, these studies focused on objectively measuring changes in patient care such as resuscitation time and task completion rate, whereas our study focuses on how broader system issues which impact patient care can be identified and addressed.

“To Err Is Human: Building a Safer Health System” is a systematic review and analysis of leading practices in Canada focused on the need to make patient safety a priority from a systems point of view. Since this report, others have elucidated barriers in the healthcare system that prevent efficiency and safety, with particular focus on communication and teamwork. System issues are problems which arise and need to be addressed at a larger corporate or institutional level rather than an individual performance level. The resolution of systems issues requires addressing the organization, training, and dynamics of healthcare providers, institutional policies, and allocation of resources to ensure health care services meet the needs of patients. In this study, we paid particular attention to system changes which included: trauma team dynamics, educational needs of health care professionals, and the organization and accessibility of various resources needed for efficient pediatric trauma care.

Trauma simulations provide an excellent opportunity to train trauma team members and to obtain feedback. Feedback can be used to address system issues, which impact the efficiency and safety of patient care. This study is a descriptive review of evaluations from Pediatric trauma in situ simulations carried out at the Emergency Department (ED) of McMaster Children’s Hospital (MCH) in Hamilton, Ontario Canada to improve pediatric trauma care, with particular focus on issues identified in our local pediatric trauma system.

METHODS

Pediatric Trauma Simulation

A series of ten pediatric trauma in-situ simulation sessions were conducted from February 2011 to January 2012 in the MCH ED trauma bays. Participants included the pediatric emergency medicine physician, trauma team leader (TTL), ED resource nurse, ED pediatric trauma nurses, pediatric resident, pediatric surgery resident, respiratory therapist, radiology technician, ED social worker (SW), anesthesia resident, child-life specialist, ED healthcare aid (HCA), ED education clinician, ED business clerk, ED clinical pharmacist, and ED pharmacy technician. The simulations were conducted in situ, meaning that the participants were not given any prior notifications about the simulation and were expected to attend as if they were on duty for a real-life trauma patient. Simulation also took place in real ED trauma bays. Simulation models included: SimNewB® Laerdal Medical, SimBaby® Laerdal Medical, Laerdal® ALS Baby 200 (Complete), and Laerdal® R-MegaCode Kid Advanced (SimPad Capable). Cases were chosen by the TTLs based on the prevalent accidental injuries specific to each season in an attempt to prepare the trauma team personnel for anticipated patient cases for that season (refer to Figure 1 for a case example). Mechanisms of injury in the case scenarios included but were not limited to: motor vehicle accidents, pedestrian injuries, cyclist injuries, falls, drowning, and diving injuries. Embedded in each case were common topics in trauma such as C-spine injury, increased intracranial pressure, femur fracture, hypothermia, hypotension, respiratory distress, and distraught family members.

The trauma director organized simulations with the assistance of two health educators. Each simulated session took an average of 30-45 minutes from the activation of the trauma code. Videos were taken of the simulations on a few occasions for review by the coordinators to address the issues of flow and optimizing room layouts.

Feedback Collection

Feedback was obtained using evaluation forms and verbal debriefing sessions. Evaluation forms (Appendix 1) were distributed to every individual who observed and participated in the simulated trauma sessions, with the option of identifying themselves at the top of the form. The evaluation form focused on three main questions: 1) what was learned from the simulated trauma session 2) what was liked about the simulated trauma session and 3) what could have been changed to make the simulation better. Open space was provided for each question asked on the evaluation form to allow free communication of ideas. A feedback and debriefing session was conducted immediately following each simulated trauma session. Participants were given an opportunity to discuss team dynamics and the performance of clinical tasks, ask questions specific to the simulated case, and suggest areas for improvement. Debriefing sessions took 15-30 minutes to complete. All participants were expected to stay. Debriefing sessions were facilitated to maintain a non-judgemental tone but kept as open as possible to allow for the free flow of comments and ideas. To encourage honest feedback, participants were given the opportunity to write down comments which were potentially uncomfortable to be shared in a group setting. Evaluation forms were reviewed immediately following the debriefing session. The trauma director and health educators used the evaluation forms to note the educational value of what was learned, address concerns, and identify areas for improvement.

Data Analysis

This study is descriptive in nature. Answers to each debriefing question were typed and deidentified. All surveys were analyzed and classified into three main concepts by the authors.

Ethics

No consent was obtained from participants as the study was conducted for quality assurance purposes. Approval was obtained from the Research Ethics Board (REB # 13216).
Table 1. Evaluation of simulated trauma sessions by all participants.

<table>
<thead>
<tr>
<th>Identified Issues</th>
<th>Resolutions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma Team Dynamics</strong></td>
<td></td>
</tr>
<tr>
<td>1. Poor communication</td>
<td>1. Educational session on closed-loop communication</td>
</tr>
<tr>
<td>2. Lack of role identification</td>
<td>2. Smocks identifying roles and responsibility [e.g. RN, RT]</td>
</tr>
<tr>
<td>3. Inadequate handover from EMS</td>
<td>3. Flow sheet designed to better document EMS handover</td>
</tr>
<tr>
<td>4. Overcrowded room (too many participants) impeding delivery of care</td>
<td>4. Work space clearly identified and taped off box for active participants</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>1. Knowledge gaps identified in many areas regarding management and equipment</td>
<td>1. Educational sessions for specific professions were offered to address the knowledge gaps identified</td>
</tr>
<tr>
<td>2. Participants requested more complex scenarios to increase knowledge</td>
<td>2. Cases with increased complexity have been used in subsequent sessions</td>
</tr>
<tr>
<td><strong>Resource Allocation</strong></td>
<td></td>
</tr>
<tr>
<td>1. Non-optimal communication with specialty services outside of the trauma team (i.e., Neurosurgery, orthopedics, and radiology)</td>
<td>1. Mobile phone connectivity and number of hand-held and hard wired phones were increased by boosting signals throughout the department</td>
</tr>
<tr>
<td>2. Limited space to fit trauma team members and medical equipment</td>
<td>2. Two new trauma bays with increased space, multiple simulations to test and improve room layout conducted before patient treated in the new spaces</td>
</tr>
<tr>
<td>3. Resources absent or inadequate: e.g. Insufficient protective materials for the healthcare professionals</td>
<td>3. Increased stock of essential items, protective equipment, Broselow™ cart. Improved utilization of human resources (healthcare aids) during trauma resuscitation to obtain materials not immediately available in trauma bay</td>
</tr>
<tr>
<td>4. Access to trauma bay impeded by doors with security restrictions.</td>
<td>4. All trauma team members mandated to contact hospital security to ensure unrestricted entry through ER</td>
</tr>
</tbody>
</table>

Quality improvement measures

Following each simulation session, participants’ comments from the debriefing session and evaluation forms were further reviewed and discussed by the organizers of the trauma simulation. Appropriate changes were introduced into subsequent trauma simulations. Knowledge gaps were identified and educational sessions were organized to address the educational needs of specific groups of members of the trauma team. These concepts were embedded into future simulations for review and practice.

RESULTS

A total of 119 evaluation forms were obtained from 10 pediatric trauma in situ simulation sessions conducted from February 2011 to January 2012. On average, 12 evaluation forms were completed per simulated trauma (range 9 – 16 per session). The main points that were shared on the evaluation forms for each of the simulation sessions are summarized in Table 1. Responses fell into three main categories: trauma team dynamics, education, and resource allocation.

Trauma Team Dynamics

Trauma team dynamics was the most prominent theme with an emphasis on communication. The feedback in terms of how well the trauma team functioned varied widely between each trauma simulation case. The following areas of concerns were repeatedly voiced: poor communication among the trauma team members, the need for closed loop communication, lack of role identification, inadequate handover from EMS, and overcrowding in the room which impeded the delivery of care.

The role of the trauma team leader (TTL) appeared to be a critical part in the functioning of the team. Trauma team members felt that the session ran very smoothly when the TTL took time at the outset of the resuscitation to clearly identify the role of each team member and give clear, audible instructions. Closed loop communication was strongly reinforced through educational sessions. This refers to a conversation where a team member takes responsibility for a request or action and clearly responds back to the original sender when the task has been completed. The wearing of smocks to visually identify the roles of trauma team members was implemented to help with task delegation and improve communication. Issues regarding inadequate handover from EMS and poor documentation in the ED resulted in the re-design of the trauma flow sheet to document the details around the original mechanism of injury. In addition, the documenting nurse was encouraged to ask questions if the required information was not clearly stated. Finally, in order to address limited space in an overcrowded trauma bay, a part of the trauma bay was taped off with red tape as an “active zone,” with this zone only to be occupied by participants providing active patient care. This way, trauma team members can carry out tasks without any obstruction, while learners can still observe from outside of the taped area.
**Education**

Overall, trauma simulation sessions were found to be an excellent educational resource for all members of the pediatric trauma team. Benefits included realistic simulation, opportunity to practice procedures, and increased familiarity with the location of available resources in the ER trauma bays. Educational sessions were organized and offered to the relevant professionals to address knowledge gaps identified in debriefing sessions. Topics included but were not limited to: how to use a level one infuser, preparing for bedside tube thoracotomy, hypothermia treatment, inotrope infusion, jet ventilation, and how to draw up resuscitation medications. Many participants felt that more complicated simulation cases provide the opportunity to learn about multiple medical conditions and trauma diagnoses. Simulated trauma sessions are an ongoing initiative, and we plan on using cases with increasing complexity as the trauma team matures and educational needs evolve.

**Resource Allocation**

In terms of understanding the local healthcare system, many participants found the in situ trauma simulations to be a very practical way to learn about resource location, and the roles and availability of different allied health professionals (SW, HCA, child life, etc.). Concerns were repeatedly voiced surrounding the space allocation in the trauma bay. Many felt that more equipment and supplies needed to be readily available in the trauma bay. This required careful utilization of our limited space to ensure that essential equipment is readily available. In response to this concern a list was compiled over a six-month period while conducting both simulations and actual resuscitations to identify items that were missing or not readily available in the room. Following this exercise, missing items were stocked or relocated closer to the trauma bay to facilitate patient care.

Many other concerns voiced during the feedback sessions were modifiable. Changes were implemented in the system as a result to improve communication, access to resources, and staff entry into the trauma bay. Mobile phone connectivity was improved and the number of available hard-wired phones was increased in the trauma bay to alleviate poor phone reception, which was recognized as one of the main factors in preventing timely communication with medical specialties outside the core trauma team (i.e. neurosurgery, orthopaedic surgery, and radiology). In addition, two new trauma bays with increased space and improved room layout were constructed. Simulations allowed us to determine the most appropriate layout of resources within this new space. As an example, the Breslow resuscitation cart was moved to just outside of the trauma bay and a new difficult airway cart was designed to be consistent with those used for OR and ICU resuscitations. New equipment was made available using wall mounted hooks and ties for items such as splints and thermometers to maximize the use of limited space. Environmental Assistants (EA) and Health Care Aide (HCA) roles were better defined to assist with checking stock and with material transportation. A nursing checklist was instituted at the beginning of each shift to ensure the trauma room was adequately equipped and restocked. All trauma members were mandated to visit hospital security to ensure unrestricted access through the ED. Keypad access was also established as delays in team member arrival were documented related to badge access issues.

**DISCUSSION**

Trauma is identified as the leading cause of mortality in the pediatric population, hence, appropriate trauma care can have a large impact on patient outcomes. The use of simulation training in trauma has been shown to improve the quality of patient care. At our centre, the in situ simulated pediatric trauma sessions were well received by the trauma team, and provided excellent quality feedback to direct a number of educational and system improvements.

Our study is unique in that we identified system issues during our in situ pediatric trauma simulation sessions and subsequently made improvements to the pediatric trauma system. Feedback forms and debriefing sessions with open-ended questions identified areas for trauma system improvement which may have otherwise gone unnoticed. Smocks for role identification of trauma team members, standardized documentation, and extra teaching sessions on communication appear to have facilitated smoother trauma care. An efficient and safe pediatric trauma system builds upon individuals who can work in a dynamic team with a clear understanding of roles and limitations. Issues such as access to the ED, poor phone connectivity, and the location of equipment were identified as barriers. These types of issues may have gone unnoticed without a focused effort to identify and improve them using our simulation project.

The utility of simulation in training for high-acute, high-risk medical conditions has been reported. Volk et al. developed a course using high-fidelity medical simulation to provide experience in decision-making and crisis resource management for airway emergencies. Participants included residents and fellows in otolaryngology and anaesthesiology, as well as nursing staff. This study found that the clinical decision-making skills and teamwork could be taught effectively using simulation. During our study period, local participants from multiple disciplines similarly perceived that trauma simulation sessions were useful for gaining skills and improving teamwork. The use of ongoing in situ simulations in our setting in collaboration with additional formal teaching sessions for procedural skills (tube thoracotomy, using level one infuser) and communication (closed loop communication) has allowed team members to further consolidate their knowledge and skills. Wayne et al. have previously demonstrated increased knowledge and retention with the use of simulation in a study that looked at educational outcomes and compliance with advanced cardiac life support resuscitation protocols. They were able to demonstrate increased knowledge retention after 14 months. Steinemann et al. conducted a prospective, cohort intervention that used human-patient simulator-based team training curriculum and compared pre- and post-training performance. The post-training survey showed significant improvements in teamwork.
rating. Objective parameters of trauma care efficiency were also recorded with a 16% reduction in the mean overall ED resuscitation time. Our study has not focused specifically on the retention rates of skills learned or efficiency in patient care times. However, objective measures of trauma efficiency and skills retention would be an interesting next topic of study from here on. Anecdotally, simulations and actual trauma cases have run more smoothly at MCH when similar cases were encountered, implying the retention of skills and improved local trauma team dynamics.

Despite all of the benefits offered by in situ trauma simulation sessions, simulation remains prohibitive in some centres due to cost\textsuperscript{14-16}. High-fidelity simulation models require a substantial initial investment and require ongoing cost in maintenance and technical support by highly qualified individuals. Based on our experience and that of others\textsuperscript{3,14-16} it can be argued that simulation-based training creates a better trauma team. A more efficient and highly skilled trauma team can potentially reduce complications and morbidity related to trauma, thereby saving money for the healthcare system in the long term. Interestingly, some insurance companies are offering a lower liability premium to anaesthesiologists and gynaecologists who participate in simulation-based crisis resource management training, as they recognize the merits of simulation training\textsuperscript{18,19}. Although there is no published economic analysis to support the cost for simulation equipment, a long-term cost benefit could be speculated due to reduced patient morbidity and improved efficiencies through simulation training. Future studies are needed to prove that investments in simulation training are justified.

In our pediatric trauma simulations, we used models that were highly realistic. The infant model allowed simulation of a wide variety of conditions ranging from a limp, cyanotic newborn to a newborn in distress. Airway simulation was designed to accommodate all aspects of airway management including endotracheal tubes (ETs) and laryngeal mask airways (LMAs). The baby model also allowed adjustment in vitals, defibrillation, pacing, cardioversion, vascular access (both intravenous and intraosseous), and anatomical traits such as fontanelles and ability to simulate seizures. Moreover, we arranged for the simulated sessions to happen in real-time (unannounced timing of the simulated sessions) and realistic settings (in ED trauma bays) in order to simulate realistic situations to the best of our ability. Role-playing included parents of the trauma victim, which added another layer of reality, as care for the family of the trauma patient is crucial to patient care.

Low-fidelity simulations are less costly; however, they may lack the reality needed for effective training for sophisticated tasks and scenarios that require interdisciplinary involvement\textsuperscript{20}. A randomized crossover trial has proven that the level of skill acquisition is the same when comparing low vs. high fidelity simulation training tools in simple technical tasks such as laparoscopic skills training. However, we were unable to find a similar comparison in teamwork oriented tasks. In fact, most studies that aimed to improve safety involving interdisciplinary team were conducted in high fidelity in-situ simulation settings\textsuperscript{21,22}. In situ simulation occurs in real-time and real settings with real people. With the addition of a high fidelity patient model and utilization of role-playing for patients’ family and relatives, our project created extra layers of reality that encompassed the medical and social aspects of trauma care.

A paragraph discussion future direction is important. You may want to touch on how anecdotally you believe feedback and incorporating said feedback improved patient outcomes but future studies need to examine objective patient outcomes. As well as other gaps that your study has now created in the literature.

**CONCLUSION:**

Pediatric trauma in-situ simulation sessions provide a realistic and valuable training opportunity for the trauma team in a low-risk environment. They can be used to facilitate numerous improvements in local pediatric trauma systems. Similar in situ pediatric trauma simulations can be reproduced in other centres with adequate simulation resources and commitment from all trauma stakeholders. Our project is one of the first to provide a review of how feedback from in situ trauma simulation sessions can be used to improve patient care by addressing local systems issues. Continued efforts such as this are required to ensure ongoing quality improvement in the field of pediatric trauma care across Canada.

![Figure 1. Case example](https://mdprogram.mcmaster.ca(md-program-research/recognition-student-research/mumj)

**Case:**

Six year-old boy dove into pool head first, did not surface. Rescued by mom, coughing, not moving arms and legs, delivered to hospital in spinal board, no C-spine collar.

**Objectives:**

1) Management of C-spine injury
2) Airway protection in C-spine injury
3) Dealing with upset child
4) Dealing with upset mom

**References**

4. Berkenstadt H, Ziv A, Gafni N et al. The validation process of incorporating simulation-based accreditation into the...
anesthesiology Israeli national board exams. Isr Med Assoc J 2006; 8: 728-733

Appendix 1.Trauma Simulation Feedback Form

Name (optional)

Date

What I learned...

What I liked...

What I would like to charge...
Advancing glioblastoma treatment with oncolytic virotherapy

ABSTRACT:
Glioblastoma is a highly invasive brain tumor with few therapeutic options for those affected. Since the 1990’s, when an oral chemotherapy drug named temozolomide was introduced, the standard of care for glioblastoma has remained largely unchanged. A pressing need for novel therapeutics has been met with innovative research that aims to tackle glioblastoma with virotherapy. The discovery of oncolytic viruses that can selectively infect and eradicate tumors has revolutionized the therapeutic landscape. Since the first proof-of-principle experiments, the number of candidate viruses being evaluated for their oncolytic activity has exploded. This opportunity has been met with cautious optimism; rigorous safety testing has ensured that only the safest and most targeted viruses progress to clinical trials. Meanwhile, several groups have been constructing immune-stimulating recombinant viruses and evaluating their potential to enhance the oncolytic virotherapy movement. Simultaneously, numerous studies are assessing the efficacy of virus administration with concomitant immunotherapies. The results have brought astounding promise to the future of a glioblastoma treatment that is eager to be translated into the clinic.

INTRODUCTION
Glioblastoma is the most lethal and most common primary brain tumor in adults1. The disease is characterized by rapid and invasive growth and a correspondingly dismal prognosis2. Approximately 1,000 Canadians are diagnosed with glioblastoma annually and undergo maximal surgical resection followed by adjuvant chemotherapy and radiotherapy3. Despite these interventions, 90% of patients experience tumor recurrence within seven months, and fewer than 5% of patients survive five years after their initial diagnosis4. In recent years, key genomic and molecular aberrations that underlie glioblastoma pathogenesis have been uncovered, aiding prognosis and casting light on therapeutically-targetable signaling pathways5. Division by clinical subtype has noted primary (de novo) tumors to frequently harbor EGFR amplification and PTEN loss, while secondary tumors that develop from lower grade astrocytoma often bear TP53 mutations, RB loss, PDGFRA amplification, and PTEN loss. Further molecular classification has identified five subtypes (classical, mesenchymal, neural, proneural, and G-CIMP), each with distinct transcriptional signatures. The same investigations have provided evidence that extensive intratumoral heterogeneity is a hurdle to be overcome in the search for tumor-specific therapies. This suggests that a multifaceted treatment approach is not only favorable, but likely necessary, to advance the current standard of care6. Indeed, novel therapies for glioblastoma have taken advantage of this idea to target multiple aspects of tumor biology using small-molecule inhibitors, immunotherapy, gene therapy, oncolytic viruses, and more, often in conjunction with radiotherapy and chemotherapy7. This review summarizes the current standard of care for patients diagnosed with glioblastoma and elaborates on one emerging biotherapeutic agent, oncolytic viruses, currently undergoing evaluation for therapeutic efficacy.
The Path to Current Therapies

The current standard of care for glioblastoma patients consists of maximal surgical resection, radiotherapy, and concomitant temozolomide (TMZ)1. While this regime extends patient survival, the mortality rate for glioblastoma remains startlingly high. However, the challenge in bringing more targeted therapeutics to the clinic is credited to several important factors: 1) intratumoral genetic heterogeneity; 2) tumor infiltration into intricate brain regions, making complete surgical resection unachievable in many cases; 3) physiological isolation of the tumor due to the blood-brain barrier; and 4) challenges identifying self-renewing glioblastoma stem cells (GSCs)6,7.

TMZ, the major first-line therapy for glioblastoma, was first used to treat primary brain tumors in 199310,11. TMZ’s cytotoxic activity comes from its ability to transfer a methyl group to DNA, with greatest anti-tumor activity observed upon methylation at the O6 position of guanine. The DNA repair response is initiated soon after but, unable to find a corresponding base, leaves long-lasting nicks in the genetic strand. These nicks accumulate and block the cell cycle at the G2-M DNA damage checkpoint, which ultimately triggers apoptosis when cells cannot proceed through mitosis. However, the enzyme O6-methylguanine-DNA methyltransferase (MGMT) plays a primary role in resistance to TMZ by transferring methylguanine’s methyl group to a cysteine residue in the active site of MGMT. Effectively, this reverses the cytotoxic lesion created by TMZ activity and allows the cell to proceed through mitosis unharmed. In line with this, the methylation status of MGMT has been correlated with responsiveness to therapy12. Indeed, glioblastoma patients with epigenetic silencing of the MGMT gene by promoter methylation were observed to have a median survival of 21 months after TMZ and radiotherapy treatment, compared to only 15.3 months in glioblastoma patients with silenced MGMT who received only radiotherapy13.

Since the introduction of TMZ, several therapeutic options have been discovered and reserved for salvage treatment after recurrence. These include bevacizumab, a vascular endothelial growth factor (VEGF)-targeting monoclonal antibody that inhibits tumor angiogenesis and vascular permeability; a PCV (procarbazine, lomustine, vincristine) cocktail with a high toxicity profile and similar mechanism of action to TMZ; and irinotecan, another chemotherapeutic that has been combined with bevacizumab to extend progression-free survival14. Despite the availability of these therapies, they have done little to extend overall survival for patients with glioblastoma, often work in only a subset of patients, and come with a host of toxicities and side-effects that reduce quality of life both during and after treatment15. Thus, while it is true that clinicians’ therapeutic repertoire has expanded, the advent of biotherapeutics, namely immunotherapy and oncolytic virotherapy, suggests that more targeted, long-lasting approaches are on the horizon.

Oncolytic Virotherapy

The first report of a genetically modified oncolytic virus (OV) being used to treat cultured glioblastoma cells was pioneered in 199116. The study used a herpes simplex virus (HSV) mutated in the thymidine kinase (TK) gene, named HSV-di8ptk, to specifically infect and kill U87 human glioblastoma cells while leaving non-dividing neurons unharmed. Since then, HSV and other candidate viruses have been further engineered to reduce neurotoxicity and enhance oncolytic activity. Notably, many of these modifications have armed OVs with immunostimulatory genes that, when expressed, enhance the host’s anti-tumor immune response9. For example, a γ34.5-deleted HSV with resulting attenuated neurovirulence has been engineered to express IL-12 to stimulate helper T cell activity and enhance glioblastoma cell killing9. Approaches such as this have been so successful that several clinical trials are evaluating the safety and efficacy of OVs in a clinical setting (reviewed in (16)).

Unlike gene therapy which employs replication-incompetent viruses to deliver genes, OVs exercise a self-amplifying effect by replicating within cancer cells, triggering cell lysis, and spreading to nearby cells16. This is possible because malignant transformation activates signaling pathways that oppose cellular antiviral responses, such as the Wnt/β-catenin and EGFR/Ras/MAPK pathways19,20. One of the most notable alterations that occurs during tumorigenesis is loss of interferon (IFN) signaling, which is normally implicated in growth suppression, recognition of viral infection, and presentation to the host immune system21. While loss of IFN signaling confers proliferative, angiogenic, and immune-evading advantages upon cancerous cells, it simultaneously impairs their ability to sense and clear viral pathogens22. This allows OVs to selectively infect and lyse cancerous cells without harming surrounding healthy cells. The resulting cell lysis contributes to the immunogenic properties of OVs by releasing tumor-associated antigens that can be recognized by the immune system and used to stimulate a long-term anti-tumor response23. Recombinant OVs have also been engineered to express molecules that augment the virus’ lytic activity and enhance the resulting immune response24. The properties of recombinant oncolytic viruses are summarized in Figure 1. A non-exhaustive list of several promising candidates for clinical OV therapy is described below and presented in Table 1.

Herpes Simplex Virus

Herpes simplex virus (HSV) is a double-stranded DNA virus with inherent neuropathism24. HSV was the first OV to be experimentally applied to the treatment of glioblastoma, and it has since undergone extensive genetic modification to attenuate its infectivity in healthy cells and enhance its oncolytic properties25,26. These modifications include mutations to the γ34.5, UL39, and ICP47 genes, which ultimately limit viral infection, replication, and viral-mediated lysis to tumor cells. In addition to enhancing selectivity, HSV variants have been armed with therapeutic transgenes that generate an anti-tumor immune response by recruiting helper T cells, reducing regulatory T cell infiltration, and inhibiting angiogenesis in the local...
An example of this is dV7Ig, a recombinant HSV expressing secreted soluble B7-1, which stimulates T cell activity and activates T cells in an anergic state. Similarly, a HSV variant expressing interleukin-12 (IL-12), named M032, and tested in a phase I clinical study promotes the tumor-killing activity of natural killer cells and cytotoxic T cells, while also interfering with tumor-induced angiogenic activity. Recently, the HSV T-Vec (talinogene laherparepvec) received FDA approval for use in advanced melanoma, highlighting the potential for this family of viruses to be adapted to other cancer types.

Poliovirus

Poliovirus (PV) is a single-stranded, positive-sense RNA virus that normally causes the human disease poliomyelitis. The virus is capable of entering cells by using capsid proteins VP1, VP2, and VP3 to bind to the PV receptor CD155 (Necl-5, nectin-like molecule 5), which has been shown to be highly expressed in glioblastoma patient explants and cell lines. Unmodified PV’s neurotoxicity further stems from the 5’ end of its genome which bears an internal ribosomal entry site (IRES) essential for viral protein translation. To test the efficacy of PV in glioblastoma, a recombinant oncolytic...
PV, termed PVS-RIPO, combines the non-pathogenic IRES from human rhinovirus type 2 with the genome of the serotype 1 (Sabin) vaccine strain of PV\(^{33}\). Together, these components dampen PV’s neurovirulence and preclude viral replication and translation from occurring in healthy neuronal cells, but not glioblastoma cells\(^{34}\). Pre-clinical studies of glioblastoma xenografts in mice demonstrate that PVS-RIPO is capable of completely eliminating tumors in vivo and promoting a host response to virus-induced tumor cell lysis\(^{35}\). Indeed, intratumoral PVS-RIPO administration is observed to induce infiltration of dendritic cells, helper T cells, and cytotoxic T cells into the tumor microenvironment\(^{35}\). Phase I trials are currently ongoing at Duke University (USA) to assess the safety and optimal dose of PVS-RIPO when delivered intracerebrally; to date, the virus has not demonstrated dangerous side effects in patients and does not spontaneously convert back to its wild-type neurovirulent form\(^{36,37}\). Recombinant PVS-RIPO has demonstrated a 24-month survival rate of 24% and has been exceptionally made rapidly available to patients with glioblastoma while it undergoes further evaluation.

Reovirus

Orthoreovirus (RV) is a member of the reovirus family and has a double stranded RNA genome. This genetic structure, along with its transcripts, rapidly causes activation of the PKR pathway upon viral entry into cells, leading to the inhibition of viral RNA translation and induction of apoptosis\(^{38}\). As a consequence, RV shows a tropism for cells with overactive Ras signaling pathways which block PKR function and allow the virus to survive in the host cell\(^{39}\). Past studies have demonstrated that over 16 glioblastoma cell lines are susceptible to RV-mediated infection and killing, making this OV a promising, and selective, therapeutic agent\(^{40}\). RV administration, like other OV therapeutics, has been tested via direct intraleSIONal injection, which is associated with several technical and safety challenges. However, a recent clinical study in patients with glioblastoma demonstrated that RV could be delivered via a single-dose intravenous drip and successfully crossed the blood-brain barrier – a first for OV delivery\(^{40}\).

Administration of RV increased leukocyte infiltration into the tumor site, which was supported by elevated mRNA levels of CCL3 and CCL4, attractants of CD4+ helper T cells and CD8+ cytotoxic T cells, in whole-tumor RNA extracts. Immunohistochemical analysis of resected brain tumor samples also revealed increased expression of apoptotic markers, such as cleaved caspase 3, in RV-treated patients, as well as programmed death-ligand 1 (PD-L1) on both RV-treated glioblastoma samples and tumor infiltrating lymphocytes. To assess the efficacy of combining intravenous RV with programmed death 1 receptor (PD1)/PD-L1 axis blockade, an immunocompetent mouse model of glioblastoma was treated with either GM-CSF/RV followed by PD1 antibody treatment, virotherapy alone, or checkpoint blockade alone. In the combination approach, mice demonstrated significantly greater intratumoral inflammatory infiltrate, which included active helper and cytotoxic T cells. Mice treated with the combination therapy also survived significantly longer than their counterparts administered either individual regimen. An initial phase I clinical trial to determine the maximum tolerated dose (MTD) of RV administered intratumorally was performed in 12 patients in 2008\(^{41}\). Impressively, no MTD was reached and there was no significant toxicity associated with treatment; in turn, patient survival was extended up to six years.

Zika Virus

Zika virus (ZIKV) is a RNA virus of the flavivirus genus, which includes West Nile virus, dengue, and yellow fever viruses. ZIKV most commonly infects neural progenitor cells (NPCs) in the developing central nervous system, which has led to an outbreak of ZIKV-induced fetal microcephaly in recent years\(^{42}\). Upon infection by ZIKV, NPCs differentiate, lose their ability to proliferate, and subsequently undergo cell death. In adults, the effects of ZIKV infection are less severe, with rare cases of meningoencephalitis and Guillain-Barré syndrome being observed. Because NPCs share similar features with glioblastoma stem cells (GSCs), ZIKV’s tropism for NPCs has been leveraged against glioblastoma\(^{43}\). In a recent study, ZIKV was found to selectively infect GSCs in vitro, inhibit their ability to proliferate and self-renew, and increase apoptotic activity. The same effect was observed when patient-derived glioblastoma samples were inoculated with ZIKV, but did not occur with normal neural tissue specimens. To test the effects of ZIKV in vivo, mouse models of glioma were infected with a mouse-adapted ZIKV strain, named ZIKV-Dakar. This led to substantial tumor regression and prolonged survival in treated mice, but did not affect the growth of non-cancerous neural cells. To enhance the virus’ safety profile, ZIKV is being engineered to bear mutations that will attenuate its ability to infect differentiated neural cells, which would make it a novel platform for glioblastoma-targeted OV therapy.

Additional Viruses

Looking beyond the viruses described above, there are several other OV candidates at various stages of either pre-clinical or clinical evaluation.

Newcastle Disease Virus (NDV) is a single-stranded, negative-sense RNA virus derived from the avian paramyxovirus 1 family. While the mechanisms underlying NDV’s oncoselectivity in glioblastoma are not well defined, it has been demonstrated to have substantial antitumor activity both in vitro and in vivo\(^{44}\). Based on these reports, NDV has been accelerated to phase I and phase II clinical trials, with Freeman et al. reporting the first phase I trial of the highly attenuated NDV-HUJ strain being administered to patients with recurrent glioblastoma\(^{45}\). The success of this trial in extending patient survival led the same group to initiate a larger phase I/II clinical trial that is currently ongoing.

Vesicular stomatitis virus (VSV) was identified as a potential OV candidate in an early study demonstrating its sensitivity to IFN signaling, thus making it a prime candidate for treating IFN-impaired cancer cells\(^{46}\). Indeed, the same group later replaced glycoprotein G, VSV’s key mediator of neurovirulence, with arenavirus glycoprotein LCMV-GP (rVSV(GP)), thus attenuating
its neurotoxicity in healthy neural tissue. This led to tumor-specific lytic activity of rVSV(GP) in both glioblastoma cell lines and mouse xenograft models of glioblastoma⁴⁷. More recently, a chimeric VSV (VSV-LASV-GPC), encoding proteins from VSV and Lassa virus, also showed selective toxicity of glioblastoma tumors in mice⁴⁸. Importantly, this virus had the capacity to migrate within the brain, specifically infect and destroy a contralateral tumor, and leave healthy tissue unharmed.

The measles virus (MV) is a negative-sense, single-stranded RNA virus that normally causes infection of the respiratory system in humans. In 2003, Phuong et al. discovered that the highly attenuated Edmonston strain of MV, typically used for vaccination, displayed antitumor activity when grown with U87 glioblastoma cells⁴⁹. Indeed, MV’s oncolytic and safety profile in animal models led to initiation of an ongoing phase I clinical trial for its safety in patients with glioblastoma⁵⁰. Recent efforts to enhance the tumor specificity of MV have engineered strains of MV expressing antibodies targeting EGFRvIII, a common mutation of the EGFR gene in glioblastoma, as well as IL-13, which targets the IL-13 receptor α2, a frequently overexpressed gene in glioblastoma⁵¹,⁵². To further augment MV’s oncolytic activity, the virus has also been combined with anti-PD-1 blockade therapy⁵³. The results of this study demonstrated a significant survival benefit conferred by the combined treatment in a syngeneic orthotopic mouse model of glioblastoma; this was attributed to an influx of inflammatory infiltrate, predominantly composed of CD8+ cytotoxic T cells. Thus, a dual immunovirotherapy approach may lead to the most efficacious and long-term response in a clinical setting.

CONCLUSION

While numerous preclinical studies have successfully treated glioblastoma using OVs, what remains is a safe, efficacious, and long-term survival response to be observed in clinical trials. In the coming years, we expect to see the results of many phase I clinical trials that are currently ongoing – the sheer volume of which holds promise that we will see successful OVs progress to phase II. Indeed, the number of viruses being evaluated as potential therapies has exploded; as repurposed oncolytic ZIKV demonstrates, these can also come from unexpected sources.

Since the first experiments using OVs, the scientific community has overcome numerous hurdles on the path to clinical viability. This is most evident in the stark contrast between initial studies which used unmodified, intracranially-administered viruses and more recent efforts that use genetically-enhanced, intravenously-delivered viruses that cross the blood-brain barrier to reach CNS tumors. Encouragingly, safety trials have rarely demonstrated adverse side effects of OV administration; the most common toxicities relate to the inflammatory response initiated upon viral infection and produce many of the same symptoms. Despite these accomplishments, several barriers still exist to the widespread adoption of OV therapy for the treatment of glioblastoma. These include developing a minimally invasive method of OV delivery, likely through intravenous administration that is successful for a range of OVs; maximizing OV intratumoral distribution in order to achieve clinical efficacy; and evading host-mediated antivirus immunity while generating antitumor immunity to provide sustained tumor control. Current pre-clinical evaluations of OVs use animal models that aim to replicate the genetic and histological changes seen in human glioblastoma. Since many of these models do not faithfully mimic the complex nature the human disease, this presents an additional challenge that often manifests in unsuccessful clinical trials. Indeed, achieving a pre-clinical model that is representative of the heterogeneous nature of glioblastoma should be a goal in parallel to OV development. An inability to overcome one or more of these hurdles has hindered OV translation in the past, leading to poor outcomes, a lack of success in pre-clinical and clinical trials, and discontinuation of particular OV approaches. These considerations will be important to bear in mind for future OV development.

One of the most important findings gained over the course of OV studies is the capacity to generate a long-term anti-tumor immune response secondary to OV infection. This has been accomplished by combining OVs with existing immunotherapies which, as studies have shown, can significantly improve the outcome of either treatment alone. Alternatively, recombinant viruses have been created to express immune-stimulating molecules, and it is likely that combining both of these approaches will generate the most efficacious, long-term response in patients. Indeed, the only OV to exist on the market today is a recombinant virus expressing GM-CSF to stimulate the immune system. T-Vec is gaining widespread adoption for the treatment of advanced melanoma, and holds promise that other cancer-targeting OVs will follow in its footsteps.

The field of OV therapy is expanding at an outstanding rate, but such rapid growth warrants a review of our mechanistic understanding of how OVs work. In this regard, many questions remain to be answered. A thorough exploration of OV intratumoral activity, optimal mode of delivery, interactions with the immune system, and integration with immunotherapy will benefit this understanding and accelerate our path to the clinic. OV therapy has gained significant momentum and will have a remarkable impact on the future of cancer treatment.

References


https://mdprogram.mcmaster.ca/md-program-research/recognizing-student-research/mumj
Advancing glioblastoma treatment with oncolytic virotherapy

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Figure 1. Summary of Key OV Modifications.

Recombinant OVs are made to selectively infect and lyse cancer cells while also stimulating an anti-tumor immune response. Past OVs have harnessed some, or all, of these modifications to enhance the virus’ oncolytic properties and optimally target glioblastoma tumors.

https://mdprogram.mcmaster.ca/md-program-research/recognizing-student-research/mumj
The efficacy of peptide immunotherapy for cat-induced respiratory allergy

ABSTRACT:
Allergen immunotherapy (AIT) can be defined as the repeated administration of specific allergens to patients with IgE-mediated inflammatory diseases, with the ultimate goal of providing protection against allergic symptoms and inflammatory reactions associated with natural exposure to these allergens. Specifically, the therapy primarily strives to establish long-term tolerance against allergens by inducing allergen-specific regulatory B and T cell responses, in addition to modulating the mast cell and basophil activation thresholds to mitigate allergic pathogenesis. AIT is conventionally administered to patients both subcutaneously and sublingually; however, additional routes of administration (ie. intralymphatic immunotherapy) are under investigation. AIT is suitable for both adults and children for a variety of allergens including pollen, pet dander, house dust mite, venom, and a number of food allergens including peanut, egg, and milk. Nevertheless, more research is needed to elucidate many of the direct mechanisms in which AIT suppresses inflammatory immune responses.

INTRODUCTION
Respiratory Allergy

The prevalence of allergic diseases, including but not limited to allergic respiratory diseases, is increasing globally, particularly in developing nations. Allergic respiratory diseases, including rhinitis and asthma, are complex inflammatory diseases associated with significant quality of life disruption, a decrease in work productivity, missed school, and increased health care costs. Allergic rhinitis (AR) is characterized by inflammation of the nasal membranes, while allergic asthma (AA) is characterized by inflammation of the large airways of the lungs. Worldwide, over 400 million people are affected by AR and over 300 million people by AA. According to the World Health Organization, the number of people with AA is expected to rise to 400 million by 2025. Furthermore, there are clear links between the upper and lower airways as AR and AA are frequently comorbid conditions. More than 80% of patients with AA also have AR, whereas around 40% of patients with AR have asthma comorbidly.

Symptoms of AR are mostly nasal and include sneezing, itching, rhinorrhea, and/or nasal congestion. In addition, AR is frequently accompanied by symptoms involving the eyes, ears, and throat, including postnasal drainage. AR is often diagnosed clinically through the results of a careful history and physical examination. AR is strongly suspected when two or more symptoms out of watery rhinorrhea, sneezing, nasal obstruction, and nasal pruritus persist for ≥1 hour on most days. The skin prick test or the serum-specific immunoglobulin E (IgE) level can be used to confirm the diagnosis. The frequency of AR increases with age, and other risk factors include positive allergy skin tests, higher socioeconomic class, family history of allergy, and being born during the pollen season.

AA is characterized by airway inflammation, remodeling, and hyperresponsiveness, and symptoms include shortness of breath, cough, chest tightness, and/or wheezing. AA is often clinically diagnosed through the results of the medical history and physical examination. The diagnosis is made when the patient reacts positively to a skin prick test and presents with episodic symptoms of airflow obstruction or airway hyperresponsiveness which are partially reversible. Confirmation of diagnosis is often done using spirometry to demonstrate obstruction and assess reversibility, in which reversibility is determined by an increase in forced expiratory volume in 1 second (FEV1) of greater than or equal to 12% from

Authors:
Jia Lu¹, BHSc[c]
Matthew Boroditsky², MD[c]
John Paul Oliveria³, PhD

1. Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
2. Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
3. Department of Medicine, Division of Respirology, McMaster University, Hamilton, ON, Canada
4. School of Medicine, Department of Pathology, Stanford University, Palo Alto, CA, United States
baseline after inhalation of a short-acting bronchodilator. Atopy, the genetic tendency to develop allergic diseases, is frequently identified as a risk factor for the development of AA. Early dust mite sensitization and maternal asthma are also risk factors of AA, while microbial exposure has shown to be inversely correlated with the development of asthma and atopy. As such, it is likely that AA develops in individuals through a combination of genetic susceptibility and environmental exposures.

The pathophysiology of AR and AA begins with sensitization to allergens (Figure 1). The presentation of processed antigen from allergen to Cluster of Differentiation (CD)4+ T cells leads to the differentiation of naïve T cells into allergen-specific type 2 Th helper (Th2) cells. Interleukin (IL)-3, IL-4, IL-5 and other type 2 cytokines produced by activated Th2 cells induce isotype switching of B cells to produce specific IgE that binds onto high-affinity IgE receptors (FcεRI) on mast cells or basophils. At this stage, IgE-sensitized individuals do not display any clinical symptoms, but the mast cells and basophils will readily release mediators upon subsequent encounters with allergen.

The allergic response in AR and AA can be divided into immediate-or early-phase response, and late-phase response (Figure 2). In the early-phase response, mediators released by mast cells and basophils cause blood vessels to leak and produce mucosal edema as well as watery rhinorrhea in patients with AR. These responses occur within minutes of allergen exposure, leading to characteristic symptoms such as sneezing, itching, and clear rhinorrhea. In the case of AA, these mediators lead to acute bronchoconstriction and airway hyperresponsiveness. Early asthmatic response develops 10-15 minutes after allergen exposure, reaches a maximum within 30 minutes, and resolves by 1-3 hours.

The late-phase response is hypothesized to be caused by mediators produced by mast cells and basophils in the early-phase response and the infiltration of leukocytes into the tissue. Congestion, irritability, and fatigue distinguish the late-phase response from the early-phase response in patients with AR. Mediators released during the early-phase response are thought to act on postcapillary endothelial cells to promote the expression of vascular cell adhesion molecule and E-selectin, which facilitate the adhesion of circulating leukocytes to endothelial cells. Furthermore, cytokines released from Th2 and other cells may circulate to the hypothalamus, resulting in symptoms of fatigue and irritability. This late-phase response occurs 4-8 hours after allergen exposure, and clinical symptoms may be similar to the immediate response but with congestion more dominant. In terms of AA, the bronchoconstriction that occurs during the late-phase response is thought to be caused by cysteinyl leukotrienes and histamine release. Cytokines released by Th2 cells lead to an increase in airway eosinophils, basophils, and neutrophils. These prolonged responses occur after 3-4 hours and could last several days to weeks. However, late asthmatic response does not always take place and occurs in approximately 60% of adults and 80% of children.

### Role of Regulatory T and B cells

Regulatory T (Treg) cells encompass a heterogeneous group of T cell subsets with suppressive capacity to impair excessive immune responses to pathogens, control the development of autoimmune and allergic diseases, and induce immune tolerance. Regulatory B (Breg) cells encompass a heterogeneous group of different immunosuppressive B cell subsets that regulate the immune system by different mechanisms. Abnormal functions or imbalances in Treg and Breg cells have been implicated in the development of allergic diseases. For example, it has been observed that in the umbilical cord blood of newborns at genetic risk of allergy, Treg cells were already defective.

Treg cells can prevent and inhibit ongoing allergic inflammation by four main groups of suppressive mechanisms—suppressive cytokines, metabolic disruption mechanisms, suppression of dendritic cell (DC) activation by membrane-bound molecules, and cytolysis. Treg cells can directly or indirectly suppress almost all cell types involved in allergic responses through these mechanisms. On the other hand, Breg cells can suppress allergic responses through suppressing effector Th cells, promoting the generation of Treg cells and tolerogenic DCs, and producing blocking IgG4 antibodies. By releasing anti-inflammatory cytokines (such as TGF-β and IL-10), Breg cells can suppress effector T cell responses and favor Treg cell induction. Through isotype switching, Breg cells are also able to produce IgG4 blocking antibodies which compete for the same epitopes (reactive sites of antigen molecules that antibodies bind) as IgE, thus inhibiting the activity of IgE.

### Treatments for Respiratory Allergy

Therapeutic options for respiratory allergy mostly focus on alleviating symptoms (Figure 3). Options such as avoidance measures, leukotriene receptor antagonists, anti-IgE antibody, and corticosteroids, by topical nasal preparations for rhinitis and inhalation for asthma, are effective methods/agents for both AR and AA. β2-agonists are specific to the treatment of AA, while antihistamines and nasal decongestants are specific to the treatment of AR. In the Allergic Rhinitis and its Impact on Asthma (ARIA) document and Global Initiative for Asthma (GINA) guidelines published in 2017, intranasal and inhaled corticosteroids are still recommended as the most effective drugs for treating AR and AA. Intranasal or inhaled corticosteroids alone usually induce few systemic side effects in patients. However, for patients with concomitant AR and AA using both inhaled and intranasal corticosteroids, and thus receiving higher doses, potential side effects may be more likely to occur. Another therapeutic approach for both AR and AA is allergen immunotherapy (AIT), but the treatment has typically been reserved for patients in which optimal avoidance measures and pharmacotherapy are insufficient to control symptoms. Unlike pharmacotherapy that alleviates mediator- or receptor-related symptoms, AIT is the only disease-modifying treatment for allergy with sustained clinical response after discontinuation of treatment.
**IMMUNOTHERAPY**

AIT is traditionally conducted with whole allergen extract and given in gradually increasing doses\(^1, 18\). The goal of AIT is to reduce symptoms of allergy by developing tolerance to the allergen in the individual\(^1, 18\). After commencing AIT, studies have shown that the susceptibility of basophils and mast cells to degranulation is reduced within hours, which is likely linked to the rapid upregulation of histamine receptor H2 (H2R) on these cells\(^17\). As opposed to histamine receptor H1, H2R is considered to induce tolerance and suppress functions of allergen-specific T cells and basophils\(^19\). Following these changes, Treg and Breg cells are generated while allergen-specific Th2 cells are suppressed\(^18\). This leads to immune deviation from a Th2 to a Th1 response with increased synthesis of IL-12 and interferon gamma (IFNγ) and decreased synthesis of IL-4\(^18\). Release of suppressive factors, such as IL-10 and TGF-β, by Treg cells also induce immune tolerance and skew B-cell production of allergen-specific IgE to IgG4\(^18\). Overall, these changes lead to sustained immunological and clinical tolerance to the allergen\(^18\).

### Routes of Administration for Allergen Immunotherapy (AIT)

Currently, approved routes of administration for AIT in clinical practice are either subcutaneous (SCIT) or sublingual (SLIT) routes\(^13, 18\). SCIT involves repeated injections of allergen extract subcutaneously to induce immunological tolerance, while SLIT involves keeping the allergen extract drops or tablets under the tongue for 1–2 minutes and then swallowing them\(^13, 18\). SCIT has been in use for many years in several countries for the treatment of AR and stable asthma, and is considered the most effective form of AIT\(^13, 18\). However, its widespread use is limited by the risks of systemic allergic reactions and the inconvenience of repeated supervised injections often over long periods in a medical facility\(^13, 18\). In comparison, SLIT is safer and has fewer serious adverse events than SCIT, allowing home administration, which is more convenient\(^13, 18\). Despite widespread use in Europe, the effectiveness of SLIT is still limited by troublesome side effects and poor adherence due to long treatment regimen and the need for daily use\(^13, 18\).

In addition to SCIT and SLIT, other routes of administration are under investigation in order to improve the efficacy of AIT\(^13, 18\). Research into oral immunotherapy has been increasing over recent years, particularly in food allergy\(^18\). The epidermis is another attractive site of research due to the presence of antigen-presenting Langerhans cells and the indirect modulation of Treg cells when the epidermis is injured\(^18\). An allergen-containing patch is the most popular form of epicutaneous immunotherapy, and has been investigated in seasonal AR\(^18\). The direct administration of allergen into lymph nodes is based on the concept that small amounts of allergen in secondary lymphoid organs may elicit significant beneficial immune changes, and has been investigated in grass pollen and cat allergy\(^18\). In addition to novel routes of administration, modification of allergens is another research focus to improve the efficacy of AIT\(^13, 18\).

### T Cell Epitope Peptides

The use of whole allergen extract faces certain problems related to its efficacy, including possible severe treatment-related reactions, low patient adherence, and long duration of treatment\(^13, 18\). In order to solve these problems, major efforts have been directed toward modifying allergen extracts\(^9, 14\). AIT with short allergen-derived peptides is an important advancement based on the induction of T cell tolerance with reduced allergenicity\(^13, 18\). Short allergen-derived peptides are carefully selected and designed to represent the dominant T cell epitopes with the removal of IgE epitopes from the whole allergens\(^13, 18\). Peptides can induce T cell tolerance more efficiently than whole allergens by directly binding to major histocompatibility complex (MHC) on antigen-presenting cells (APCs) in the absence of pro-inflammatory signals\(^13, 18\). This allows peptide immunotherapy to induce clinical tolerance to allergens in a much shorter time frame than whole allergens and without allergic side effects\(^13, 18\). Similar to conventional AIT, the mechanisms of action for peptide immunotherapy involve immune deviation and induction of Treg cells\(^13, 18\). In the absence of pro-inflammatory signals, peptide immunotherapy also exploits a tolerance pathway, leading to specific T cell anergy and allergen-specific Th2 cell deletion\(^13, 18\).

The concept of peptide AIT was first introduced in the 1990s, when non-responsiveness of T cells to whole dust mites was induced through short-term incubation of clonal Der p 1-specific T cells with high concentration of a dominant T cell epitope peptide of Der p 1 (a major dust mite allergen epitope)\(^18\). Since then, research into T cell epitope peptides has been expanded to several allergies, including grass and cat allergy\(^13, 18\). Fel d 1 is a major cat allergen epitope which reacts in over 90% of cat-sensitized individuals, and the prevalence of cat sensitization ranges up to 15% in some areas of northern Europe\(^1, 2, 20\). Animal studies and placebo-controlled clinical trials have been conducted to assess the efficacy of T cell epitope peptides in treating cat-induced respiratory allergy\(^13, 18, 21-31\).

### Animal Studies

In transgenic mice with the human MHC class II molecule and lacking endogenous mouse MHC class II, Campbell et al. treated the mice with a specific Fel d 1 peptide to examine the local allergen-specific T cell response within lung tissue\(^22\). Compared to control (influenza hemagglutinin peptide), treatment with Fel d 1 peptide reduced total leukocyte and eosinophil recruitment to the lung, thus reducing lung inflammation and improving lung function\(^22\). A significant increase in IL-10, produced by allergen-specific Treg cells, was reported in lung tissue following peptide AIT\(^22\). Blocking the peptide-induced effects with the administration of an anti-IL-10 monoclonal antibody after treatment further demonstrated that IL-10 is a critical cytokine in the resolution of allergic lung inflammation\(^22\).
The Fel d 1 allergen consists of two disulphide-linked heterodimers of chains 1 and 2. Earlier studies in subjects with respiratory allergy to cats were conducted with two 27-amino acid peptides, called IPC-1 and IPC-2, from Fel d 1 chain 129-31. These synthesized peptides contained dominant T cell epitopes and were licensed as Allervax CAT. In the first trial, 95 cat-sensitized patients were blinded and randomized into receiving placebo, 7.5 µg, 75 µg, or 750 µg of Allervax CAT23. Six weeks after weekly subcutaneous injections for 4 weeks, improvement in lung and nasal symptoms scores were observed in patients who received higher doses of Allervax CAT23. However, treatment with higher doses was associated with many allergic side effects which occurred an hour or more after29. In a randomized double-blind placebo-controlled (RDBPC) trial, patients who received four subcutaneous weekly injections of 250 µg Allervax CAT did not tolerate significantly more cat extract in skin tests than controls24. In another RDBPC trial involving patients receiving eight subcutaneous injections of 750 µg Allervax CAT, improvement in pulmonary function was only evident at a single time point after treatment25. Due to high incidence of adverse events and non-superior clinical outcomes to conventionalAIT, development of Allervax CAT was halted29.

A second generation of synthetic T cell epitope peptides (Cat-SPIRE / Cat-PAD) was developed and comprised seven separate small peptides, derived from Fel d 1 chains 1 and 2, which bound to commonly expressed human leukocyte antigen-D related (HLA-DR) molecules27-31. Compared to first generation peptides, Cat-SPIRE are much shorter, such that they do not trigger cross-linking of IgE on basophils and mast cells27,29. In a RDBPC escalating, single dose trial, Worm et al. injected 88 patients, either intradermally or subcutaneously, with 0.03 – 12 nmol of Cat-SPIRE and measured late-phase skin reaction as a surrogate marker for clinical efficacy27. In the intradermal group, a 40% reduction in late-phase skin reaction was observed at 3 nmol, and although none of the changes in reaction were significant, there was a trend toward significance at 3 nmol27. Smaller reductions and more adverse allergic symptoms were observed in the subcutaneous group27. As such, intradermal was proven to be superior regarding tolerability and selected as the route of administration for later clinical trials27,32. In a RDBPC phase 2 study, patients were randomized into two active groups: 4 intradermal doses of 6 nmol given 4 weeks apart or 8 intradermal doses of 3 nmol given 2 weeks apart30,31. The treatment effect was apparent at 18 – 22 weeks, and the reduction in symptom severity in the 6 nmol group was significantly different from the placebo and 3 nmol groups at 1 year30. In the subsequent follow-up study, a greater reduction in symptom severity was observed in the 6 nmol group compared to placebo 2 years after the start of treatment31. Results from the phase 2 study highlight the effects of dosing and frequency of dosing on the efficacy of treatment.

**LIMITATIONS**

The phase 3 clinical study for Cat-SPIRE was completed in June 2016. In this RDBPC trial, patients were randomized into three groups: 4 intradermal doses of 6 nmol Cat-SPIRE followed by 4 injections of placebo given 4 weeks apart, 8 doses of 6 nmol Cat-SPIRE given every 4 weeks, or 8 doses of placebo given 4 weeks apart30-34. Although the results have yet to be published, it was announced that the primary endpoint, a difference in combined score of symptoms and allergy medication use between the treatment and placebo one year after the start of treatment, was not achieved35.

**FUTURE DIRECTIONS**

To reduce T cell-dependent side-effects, some researchers are looking into developing B cell epitope–based allergy vaccines66,67. This type of immunotherapy uses genetically engineered non-IgE-reactive peptides (between 20 – 40 amino acids) derived from or close to the IgE-binding sites of the allergen that do not contain T cell epitopes66,67. Conceptually, these peptides will not cross-link effector cell-bound IgE and will have no or minimal T cell reactivity66,67. Hence, these peptides should not induce immediate allergic inflammation or T cell-dependent side effects66,67. Furthermore, the use of a strongly immunogenic carrier (a protein carrier that is covalently linked to the peptides and not related to allergens) should induce allergen-specific IgG responses, which strongly block IgE antibodies from binding to the allergen66,67. B cell epitope–based allergy vaccines are a new area of research and hold potential to improve the efficacy of AIT in treating Fel d 1-induced respiratory allergies66,67.

Additionally, a team in Switzerland is researching the vaccination of cats and dogs against the allergens they produce38. Specifically, for cat-related allergies, the team is looking to vaccinate cats against the allergen Fel d 1 and sensitize them to the allergen, thus rendering them hypoallergenic through the immune destruction of Fel d 1 in the cats’ body38. Fel d 1 appears not to be of critical importance for cats so the vaccination will not harm the cats38.

**CONCLUSION**

Allergen immunotherapy, with research spanning over a century, is a well-established therapy with a primary goal of inducing natural suppressive immune responses upon subsequent allergen exposure and decreasing inflammatory, allergic responses. Although there are many fundamental regulatory mechanisms at play that contribute to the desensitization process during allergen immunotherapy, more research is still needed in this field, particularly in the immunological, cellular and molecular mechanisms inducing tolerance. However, the results published thus far are promising, and the research community needs to push forward in their research ventures so that the millions of people affected by cat-induced allergic exacerbations can be treated and managed accordingly.
References


The efficacy of peptide immunotherapy for cat-induced respiratory allergy


List of Abbreviations:

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AR</td>
<td>allergic rhinitis</td>
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<td>AA</td>
<td>allergic asthma</td>
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<td>AIT</td>
<td>allergen immunotherapy</td>
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<td>IgE</td>
<td>immunoglobulin E</td>
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<td>FEV₁</td>
<td>forced expiratory volume in 1 second</td>
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<tr>
<td>DC</td>
<td>dendritic cell</td>
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<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
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<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
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<tr>
<td>CD</td>
<td>Cluster of Differentiation</td>
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<tr>
<td>Th2</td>
<td>type 2 T helper</td>
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<td>IL</td>
<td>interleukin</td>
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<td>FceRI</td>
<td>high-affinity IgE receptors</td>
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<td>regulatory T cells</td>
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<tr>
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<tr>
<td>TGF-β</td>
<td>transforming growth factor beta</td>
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<td>ARIA</td>
<td>Allergic Rhinitis and its Impact on Asthma</td>
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<td>GINA</td>
<td>Global Initiative for Asthma</td>
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<tr>
<td>H₂R</td>
<td>histamine receptor H2</td>
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<td>IFNγ</td>
<td>interferon gamma</td>
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<td>SCIT</td>
<td>subcutaneous immunotherapy</td>
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<td>SLIT</td>
<td>sublingual immunotherapy</td>
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<tr>
<td>RDBPC</td>
<td>randomized double-blind placebo-controlled</td>
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<tr>
<td>HLA-DR</td>
<td>human leukocyte antigen-D related</td>
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**Figures**

**Figure 1.** Immunological mechanisms underlying allergic sensitization.

Dendritic cells in the mucosal surface or airway lining process inhaled allergens and present processed antigen via MHC class II molecules to CD4+ T cells in lymph nodes. This results in the differentiation of naïve CD4+ T cells to allergen-specific Th2 cells. Activated Th2 cells release IL-3, IL-4, IL-5, and other type 2 cytokines, which drive pro-inflammatory processes by inducing isotype switching of B cells to produce antigen-specific IgE as well as infiltration of mast cells, neutrophils, and eosinophils. Secreted IgE binds onto high-affinity IgE receptors on mast cells or basophils, thus leading to the IgE sensitization of individuals against the allergen. DC: dendritic cell; Th: helper T cell; IL: interleukin.

**Figure 2.** Early- and late-phase responses in allergic rhinitis and asthma.

The early-phase response is due to subsequent cross-linking of IgE by allergen, causing mast cell degranulation and the release of mediators such as histamine, prostaglandins and leukotrienes. In the late-phase response, Th2 cells release chemoattractant cytokines, such as IL-5, promoting the infiltration of eosinophils, basophils, and neutrophils into the area. Upon infiltration, these cells release inflammatory mediators and reactivate the reactions of the immediate response. Th: helper T cell; IL: interleukin; AR: allergic rhinitis; AA: allergic asthma.

**Figure 3.** Common therapeutic options that focus on alleviating symptoms for allergic rhinitis and asthma.

Allergic Rhinitis
- Anti-histamines
- Nasal decongestants

Allergic Asthma
- β2 agonists
- Avoidance measures
- Leukotriene receptor antagonists
- Anti-IgE antibody
- Corticosteroids

Both
- Both options
INTRODUCTION

Severe obesity is a chronic disease and is defined as a BMI greater than 35 with comorbid health conditions, or a BMI greater than 40 without comorbidities. It increases morbidity, premature mortality, impairs quality of life, leads to excess healthcare spending, and increases the risk of developing type II diabetes mellitus, micro and macrovascular complications. Conservative treatment measures commonly used for severe obesity, including lifestyle modifications and pharmacotherapy, often fail in the long term.

An important and under-discussed tool to treat severe obesity and diabetes is bariatric surgery. Bariatric surgery generally consists of surgeries which either limit the size of the stomach (restrictive procedures), bypass part of the small intestine (malabsorptive), or both. The two main procedures performed in Canada are the sleeve gastrectomy, which creates a tubular stomach, as well as the Roux-en-Y gastric bypass, which creates a small gastric pouch and bypasses part of the intestine. Bariatric surgery also has a substantial role in diabetes treatment, prevention and cancer risk reduction, specifically for obesity-related cancers. The role of bariatric surgery in adolescents and the effects on pregnancy outcomes has also been shown but are not fully delineated at this point. Full mechanisms as to how it works, especially in relation to diabetes, are still being elucidated but hormonal shifts in addition to changes to the gut microbiology are chiefly implicated.

In addition, the demand for bariatric surgery to treat severe obesity is growing rapidly in Canada. According to a 2014 Canadian Institute of Health Information (CIHI) report, there were nearly 6000 bariatric surgeries performed across Canada which is nearly four times the number of bariatric procedures done in 2006-2007. Almost half of these surgeries were performed in Ontario. Currently, the rate of bariatric surgery in Canada is one-third of that in the United States with only approximately 1 of 1000 eligible patients receiving the surgery. This lack of access has driven many patients to pay out of pocket for bariatric procedures or incur significant costs to travel to the limited centers that offer these procedures. This is particularly relevant to primary care physicians since they face the challenges of treating obesity on a daily basis. As well, primary care physicians are often tasked with the long-term postoperative management of bariatric patients. As such, this commentary will provide an overview of the current evidence for bariatric surgery and discuss the need for greater exposure to bariatric surgery within medical education.

Bariatric surgery

Bariatric surgery is the most effective long-term treatment option for weight loss. In the latest long-term randomized cohort study following 1156 patients after gastric bypass, Adams and colleagues have demonstrated that 12 years after surgery, mean weight loss in the surgery group was 35 kg, compared to losses of 2.9 kg and 0 kg in the two nonsurgical groups. This was replicated in another study by Maciejewski and colleagues which followed 405 patients undergoing Roux-en-Y gastric bypass surgery over 10 years, and found that 71.8% maintained 20% or greater weight loss. These long terms results demonstrate the superiority of gastric bypass surgery as an effective method for weight loss in the severely obese population.

Bariatric surgery is also the most effective treatment for Type II diabetes and has a substantial effect on Type II diabetes prevention. In a recent study by Adams and colleagues, Type II diabetes remission rates were 51% at 12 years with gastric bypass. This means a controlled HBA1C without the use of medications. As well, the odds of incidence of diabetes was more than 90% lower in the bariatric surgery group. In 2016, the American Diabetes Association declared...
Bariatric surgery also reduces the risk of obesity related cancer. After a mean follow-up of 3.5 years in a matched-cohort of 22,198 surgical patients and 66,427 controls, the hazard ratio of obesity related cancers was 41% lower in the surgery group. Cancers included postmenopausal breast cancer, colon cancer, endometrial cancer, and pancreatic cancer. Furthermore, the results were most pronounced for endometrial and postmenopausal breast cancer, likely related to the decrease in circulating estrogen with weight loss. These results persisted for the duration of the 10-year follow up for the study.

In addition to adults, bariatric surgery is effective in adolescents but further study is required. In a recent cohort of 242 adolescents, mean weight loss was 27% and the remission rates of diabetes, abnormal kidney function, elevated blood pressure and dyslipidemia were 95%, 85%, 74% and 66%, respectively. However, there were risks of micronutrient deficiencies and the possibility that future abdominal procedures may be needed.

Finally, bariatric surgery has positive effects on pregnancy outcomes. A recent study by Johansson and colleagues demonstrated that the odds of gestational diabetes and large-for-gestational-age were 75% and 67% lower in the bariatric surgery group compared to matched controls. Conversely, small-for-gestational-age infants and shorter gestation (4.5 days) was observed. Preterm birth and the risk of stillbirth or neonatal death were not significantly different between groups. Notably, the vast majority of patients undergoing bariatric surgery in Canada are women within their reproductive years. In 2012, 80% of bariatric surgery patients across Canada were women and 65% of the total patients (both male and female) were under the age of 50.4 Subsequently, several authors have discussed the importance of understanding the unique challenges of antenatal care and to ensure adequate and timely follow up for patients. In a recent review, Griffith and colleagues examined both early and late postoperative complications following laparoscopic roux-en-y gastric bypass and discussed common approaches to managing these complications including anastomotic leak and postoperative hemorrhage. However, considering the effect of gastric bypass on long-term mortality and morbidity, bariatric surgery remains an important intervention for patients with morbid obesity.

Bariatric Surgery in Medical Education

Despite the growing body of literature highlighting the importance of bariatric surgery in various illness outcomes, research in the area of medical education demonstrates a glaring lack of adequate training in obesity treatment. In a US study, Stanford and colleagues evaluated the knowledge base of primary care physicians (including family physicians and internists) related to obesity and bariatric surgery and found that those who had received more than one hour of obesity training during medical school felt more confident providing obesity care and were more likely to answer questions regarding obesity management correctly. Salinas and colleagues also demonstrated that physicians with more knowledge and positive attitudes toward obesity management as well as greater access to resources were more likely to manage obesity in the primary care setting. Furthermore, a 2012 review of obesity educational interventions in US medical schools found that there are very few published studies examining the effectiveness of obesity education in medical school curricula. As there is a noted gap in the Canadian literature in this area, US data are utilized in this commentary acknowledging the limitations of population differences and variability of accessibility to bariatric surgery between these two contexts.

As senior medical students at McMaster University, and having completed the pre-clerkship curriculum, as well as rotations in general surgery, internal medicine, and family medicine, there has been no formal teaching on the benefits of bariatric surgery as a treatment option for severe obesity and diabetes. Review of outlined pre-clerkship topics on the McMaster student portal verifies that there is no mention of bariatric surgery throughout the pre-clerkship curriculum. As well, there is no clinical or surgical exposure to weight loss clinics or bariatric surgeries, unless students schedule electives in these specific subspecialties. Consequently, at the time of graduation, students tend to lack exposure to this topic. Though some innovative pilot programs in obesity education have been carried out at the medical school level, for example, pairing students longitudinally with obese patients undergoing bariatric surgery, the longitudinal impact of such programs on physician attitudes and approach to practice have not been examined.

According to a recent report by the Canadian Obesity Network, factors delaying treatment for obesity, including bariatric surgery, include the
following: obesity has not been verified as a chronic disease, obesity is treated as a self-inflicted illness, there are no real official guidelines for obesity management, education around obesity is provided as self-management programs, there is a lack of interdisciplinary teams and trained physicians with interests in obesity management, there is poor funding for anti-obesity medication and diets, there is poor access to bariatric surgery, and long wait times between referrals and consultations for bariatric surgery. In Ontario, the average wait time between referral and consultation is up to two years, and between consultation and surgery is six to 12 months. Given the long wait times for surgery and the significant role played by primary care providers in the care of obese patients, health professionals at all levels of care require adequate training in obesity management.

CONCLUSION

Obesity is a growing epidemic in Canada leading to increased morbidity and mortality. Though bariatric surgery is recognized as the optimal treatment to improve outcomes, greater training is needed for medical students and primary care physicians. Furthermore, there is a paucity of Canadian data regarding short- and long-term efficacy of obesity training for primary care providers. The growing population of morbidly obese Canadians, however, demands deliberate and specific medical training related to obesity and bariatric surgery.

References

Public health, risk discourse, and osteoporosis: A critical assessment of osteoporosis prevention in Ontario

Authors:
Alyson Holland¹, PhD

1. McMaster University, Hamilton, Ontario, Canada

INTRODUCTION
Since the 1980s osteoporosis has been viewed as a public health crisis in North America¹. The concern over osteoporosis has intensified in recent decades due to an aging population, which has created a greater focus on osteoporosis prevention and management approaches carried out by public health organizations. Public health in North America is grounded in risk-based epidemiological models that are used to identify what populations or groups are in need of prevention. Risk-based approaches have been common since the emergence of the “new” public health after the first world war. A reimagining of public health was driven by the constant threat of risk posed by environmental hazards and the growing awareness of lifestyle risks in the health literature. In order to be effective public health had to fundamentally reorganise itself around risk prevention and communication². This included the translation and dissemination of expert knowledge on health risk into lay language that could then be used by the public to adopt healthier behaviours³. This risk communication is now termed health promotion, an education-based method of translating health knowledge through engagement with communities and individuals.

As public health has expanded its mandate, the consequences of a public health approach to population health have grown. While there is no question that increased efforts toward health are beneficial to populations, there are inherent problems in the framework on which the public health approach is based. The main problems with using a risk-based system is that risk is actually a statistical method designed for populations, not individuals⁴-⁶. Risk as synonymous with danger or harm is how risk is used in a public health context and has come to be understood as the potential for disease or ill health⁷,⁸. Individuals are concerned about their own personal risk of disease and so public health attempts to translate population level data into individual risk⁹-¹¹. As a result, public health has taken on the role of risk translators and communicators for the public.

While risk-based models are generally accepted as the norm for public health because they lead to positive reductions in disease, they also have recognized negative effects on individuals and populations¹²,¹³. Discourses within public health often uncritically promotes the use of risk-based models, without due recognition of their limitations. This is not to suggest that these models do not work, as many have proven effective in reducing overall disease rates. However, the unexamined acceptance of these models within the literature creates a space in which the negative effects of these models are not addressed by those implementing them, which in turn raises the possibility that some people may be harmed by their use. This issue can be seen in osteoporosis health promotion, where the World Health Organization serves as the guide in prevention and management that is designed within this epidemiological, risk-based approach. Osteoporosis is currently viewed as an entrenched public health crisis, brought on by an aging population that this living longer. The need for osteoporosis prevention is growing, leading to widespread dissemination of risk-based prevention models for which the negative effects have only been cursorily examined. The purpose of this paper is therefore to use a critical medical anthropology lens to assess the application of a risk-based public health model to osteoporosis in order to gain a more nuanced understanding of the effects of risk-based models within osteoporosis promotion.

Public health and osteoporosis: A case study

Osteoporosis prevention initiatives in Ontario

Osteoporosis health promotion occurs at the national, provincial and local levels in Canada. At the national level, osteoporosis promotion and prevention is carried out primarily by Osteoporosis Canada (a non-governmental organization), which often collaborates with the Public Health Agency of Canada and Health Canada on the development of osteoporosis information¹⁴. Osteoporosis surveillance is managed by the Public Health Agency of Canada’s (PHAC) Center for Chronic Disease Prevention and Control and Health Canada¹⁴. Osteoporosis Canada, which is associated with the International Osteoporosis Foundation (IOF), is active in public health promotion throughout Canada at the national, provincial and local levels through specific provincial and locally-based initiatives.

In Ontario, osteoporosis prevention is shared by Osteoporosis Canada and the Ontario Osteoporosis Strategy. The Ontario Osteoporosis
Strategy is a joint venture of the Ministry of Health and Long-Term Care (MOHLTC), the Ontario Women's Health Council, the Ministry of Education, the Ministry of Health Promotion, Osteoporosis Canada, the Dairy Farmers of Canada and a number of hospitals throughout Ontario. The Ontario Osteoporosis Strategy is an active initiative that provides education and support to specific target groups that include men and women over 40 and grade five students in Ontario schools. At the local level, Osteoporosis Canada has a number of chapters which follow the national mandate but operate essentially independently. These chapters deliver the national health promotion programs including: the ‘speaking of bones’ community outreach speakers program; the ‘BoneFit’ exercise initiative; participation in the Canadian Osteoporosis Patients Network (COPN), a national support network for osteoporosis patients; and the “Break Through” educational program. However the chapters tend to tailor their prevention programs to the community, with the goal being to provide the type of education and activities desired by the community. As a result there is considerable variability between programs. While these are the main organizations that deal specifically with osteoporosis health promotion, osteoporosis is also covered under other initiatives that deal broadly with chronic disease.

Canadian osteoporosis health promotion initiatives are based on the standards established by the WHO and the IOF. In keeping with the changes in the new public health, osteoporosis health promotion is centered around empowerment of individuals to take control of their own health. Osteoporosis education is risk-centered, with a focus on identifying individuals who are at high risk of fractures and delivering preventative education and support to change individuals’ health behaviours and prevent fractures. The large number of risk factors that are outside the control of the individual results in osteoporosis education being focused narrowly on the few factors that individuals can control, generally diet and exercise. Vigilance and self-surveillance are common themes and individuals are encouraged to communicate with their physicians about their bone density, monitor their calcium and vitamin D intake, and exercise regularly in order to build bone and maintain muscles for balance. These themes are seen on the information webpages for Osteoporosis Canada, PHAC and Health Canada. The underlying theme in osteoporosis promotion is that individuals must actively seek out education in order to manage their risk factors and the responsibility for osteoporosis management is on the individual.

The Ontario Osteoporosis Strategy is concerned with access to bone mineral density testing and education on osteoporosis. Screening for potential osteoporotic conditions and management of existing conditions require the use of bone mineral density tests to track changes in bone. One component of this strategy focuses on treatment, which provides access for all Ontarians at specific fracture clinics that are trained in the treatment of osteoporosis. Other components involve education programs for 5th graders, the widespread dissemination of osteoporosis education information to the general public through commercials and to specific high risk groups through targeted education.

Socioeconomic status and prevention

What emerges from this strategy is an attempt to provide equitable access to treatment options and education for those at risk, however, the major focus of prevention is on lifestyle factors. This becomes problematic as it operates on the assumption that all people have the same capacity to engage in prevention. In doing so it does not address the broader social determinants of health. Similarly, Osteoporosis Canada, beyond providing osteoporosis education and support through its chapters, does not offer tailored prevention programs to people of low SES or differential access. This means that, while these initiatives might recognize the role that larger social processes play in placing people at risk—a theme which comes across in osteoporosis literature—they are not providing promotional programs that address or include sources of risk beyond lifestyle.

Considering the current aim of public health promotion is on addressing the social determinants of health, these osteoporosis programs fall short of their mark. While they create spaces for specialised treatment and establish routes of referral that narrow the care gap in osteoporosis, they are not focussing on bringing accessible prevention information to those at risk of osteoporosis. The issue of access to prevention education is especially concerning in rural areas where people must rely on family practitioners and community health teams to disseminate this information. Previous research on the osteoporosis knowledge of rural primary care physicians has shown a lack of confidence in osteoporosis diagnosis and management. These issues suggest that osteoporosis prevention programs need to be examined with a critical eye to assess how well they are meeting the intended goals of health promotion. Most of the information on program efficacy has been gathered from treatment of fragility fractures and involves delivery of follow up care, changes to BMD, and recurrent fragility fractures. While important in building treatment models, these measures do not accurately measure the effectiveness of prevention programs in preventing fragility fractures or decreases in BMD.

Risk factors, modelling risk, and blame

In an epidemiological model the risk factors for osteoporosis include: being female, over age 65, history of previous fracture, family history of fracture, smoking, excessive consumption of alcohol (three or more drinks per day), early menopause, low body weight (under 132 lbs), a history of falls, infrequent exercise and a diet low in calcium and vitamin D. Under a risk-based model these factors can be divided into three types: extrinsic/environmental, intrinsic/lifestyle and embodied. Extrinsic/environmental risks are those that are judged to be external and beyond the control of individuals. Intrinsic/lifestyle risks are internal risks, over which individuals do have control. In the health literature, ‘lifestyle’ risks are the result of lifestyle decisions made by individuals. The first type, embodied risks, which are internal to the individual. Embodied risks represent the body posing a physical or psychological threat to itself. Using this model, osteoporosis
falls within multiple risk categories. Many of the risks posed by osteoporosis are outside the control of individuals, but others, such as physical activity and diet, are lifestyle risks. Osteoporosis could also be considered an example of embodied risk, as defined by Kavanagh and Broom (1997), because the threat to the individual comes from the body itself. How osteoporosis is conceptualised is important because internal risks are perceived as within a person’s control and are associated with a greater amount of blame. This becomes important in health promotion where the internal risks are viewed as most easily modifiable and are given the most attention. By placing the emphasis on risks that are controllable, this creates a situation where individuals who cannot or will not modify their diet or exercise become perceived as partially to blame for their disease.

The risk that lifestyle behaviours truly pose to osteoporosis is a complex issue. While lifestyle is known to affect bone health, it represents a small fraction of the number of factors that contribute to osteoporosis. Since the other factors remain outside the control of the individual, osteoporosis prevention centers around diet and exercise. The importance of risk-reduction through these lifestyle changes is heavily emphasized, which places individuals who do not make changes in a potentially untenable role, but also offers a measure of perceived control over an embodied threat. Through lifestyle changes, individuals are provided with a mechanism to assert control over and minimize their perceived risk of osteoporosis. This implied control confers a moral responsibility on individuals to engage in behaviours that are beneficial to their health and to make efforts to minimize unhealthy activities. Health is understood to be one of the most important values in society and attaining it is seen as a moral duty. Good citizens are healthy citizens, so to reject a healthy lifestyle is to reject the ideals of Western society.

Placing lifestyle risk in the context of health access

The focus on lifestyle that is taken in public health fails to take into account the role of barriers to health access and so unintentionally labels individuals as unwilling to engage in health behaviours, rather than unable. These are often not conscious labels, but are found inherently in how public health promotes health prevention. While the new health promotion recognises the existence of social, political and economic barriers, there are no exemptions offered for those who are limited by access. Women who are unable to make the lifestyle choices they have been educated about due to barriers have the potential to feel guilty and depressed. Dietary changes involve access to leafy green vegetables, increased dairy intake, and regular meals. Following these suggestions means having access to grocery stores, both geographically and being able to physically access them, as well as having the resources to purchase these foods and the time needed to prepare them. Dairy-based foods and vegetables are costly to purchase and have a limited shelf life. Supplements are also raised as a possibility but these are also expensive and often out of reach for older adults on a limited income, which also represents the most at risk population.

Physical activity represents a similar problem. Access to a gym or to home exercise equipment requires economic means as well as time to dedicate to physical activity. Specialised osteoporosis exercise programs such as Osteo-circuit and Bonefit exist in Ontario, but come with a cost. Some programs are offered at a lower cost at the YMCA, but this still requires a financial output that is not accessible to all. This puts a strain on individuals who have access to prevention education and want to participate in risk-modifying behaviours but have limited access to them. The urge to engage in risk reduction is culturally embedded as part of the healthism and wellness culture in the west. The inability to participate not only makes people feel bad that they are actively choosing to be risky, but also draws their attention to their lack of participation, which can increase their sense of their own risk and lead to new stress.

Overarching all of the problems affecting access to these modifiable risk factors is the controversy surrounding these recommendations in the first place, as there is no concrete evidence that shows that increased physical activity or calcium and vitamin D intake have a measurable impact on fracture risk. The conflicting information provided to individuals, combined with the pressure to make good health decisions, leads to difficulty in deciding which initiatives they should be following.

Negative effects of constructing targeted prevention

How and where prevention education is presented has important implications for how the public comes to perceive their risk. Most official support for osteoporosis concerns the curative treatment of fractures, with individuals being responsible for the bulk of their prevention activities. Prevention is overwhelmingly based on targeted education to prevent additional fractures in adults with one or more fractures, to older adults who are identified as at risk due to age and/or sex, and to young children in critical growth periods. By targeting these individuals as at-risk, it serves to reinforce the fear of osteoporosis in the target groups, while causing other individuals to underestimate their own risk. While targeted osteoporosis prevention provides useful information to older adults, such as information on fall prevention, it also reinforces the role of the self in preventing osteoporosis. Placing the responsibility for risk prevention on individuals can be overwhelming for some women and act as a barrier to the adoption of health behaviours.

Targeted education also reinforces the cultural models associated with osteoporosis, which has further implications for how individuals come to perceive their osteoporosis risk. The association between osteoporosis and aging results in younger individuals underestimating their risk of osteoporosis because they do not believe it poses a risk until they are older. The reality, that osteoporosis is a lifestyle disease that is affected by risk factors established throughout life, exists in opposition to a dominant discourse on osteoporosis that places it as a natural part of aging. This dominant discourse is reinforced by education programs that target older persons. At the same time, constructing osteoporosis as a natural process also serves to minimize the sense of risk experienced by older persons. While osteoporosis is
a serious condition, individuals do not perceive it as such because it is seen as natural and expected. A similar problem is seen in men who do not perceive themselves at risk of osteoporosis because osteoporosis is understood to be a women's disease. Due to cultural construction of osteoporosis risk as dominated by women, a construction that is reinforced through the media, men who develop osteoporosis must contend with the psychological reality of having a 'women's' disease. Public awareness campaigns generally feature older women, rather than men, which can be seen in a series of public videos from Osteoporosis Canada. Similarly, osteoporosis literature shows mostly women, though there is a concerted effort within Osteoporosis Canada to change this view. Male-specific images, literature, and even events are being proposed in order to highlight the risk to men. Still, the majority of attendees at Osteoporosis Canada events are women. Men who are diagnosed tend to have more severe disease and a greater number of fractures at the time of diagnosis. This has been suggested to reflect the effects of cultural constructions of osteoporosis on the medical community, as health care providers are slower to suspect osteoporosis in men.

Medicalization and control of healthy bodies through screening

In order to control the economic problems posed by osteoporosis, the Ontario Osteoporosis Strategy introduced a screening program for osteoporosis available as a prevention method for individuals that have a large number of risk factors. Screening programs as prevention have created a large amount of debate because they bring healthy individuals into the system of medical surveillance and have the potential to increase worries about health by categorizing them into a pre-disease or disease state. Because public health approaches used risk-based models to understand disease, risk becomes a medicalizing force that can transform pre-disease states into illness. At-risk bodies require constant monitoring and management by medical institutions, which creates a system of increasing medical surveillance. This is seen in the case of low bone mass (previously osteopenia), which is a pre-osteoporotic condition and is considered to indicate a high risk of developing osteoporosis. While the individual with low bone mass does not actually have osteoporosis and might never develop it, low bone mass has come to be recognised as a disease state and confers the same threat and fear associated with a disease. The result is that more and more bodily states are seen as representing the disease and health itself becomes more difficult to attain as pre-disease states become labelled as diseases. This concern can be seen with osteoporosis screening where the process of being sent for the BMD test and having their risk assessed revealed an embodied risk and not only increased their worry about future illness and caused them to seek out further surveillance, but created a sense of alienation of the self and body.

Other concerns about screening programs have revolved around the idea of government control of bodies. Screening is seen as a mechanism to draw individuals into the web of expert knowledge created by public health in order to encourage particular behaviours. Labelling individuals at-risk because of screening, serves to instil a deeper need to comply with health information in order to avoid further ill health. Those who are screened as high risk are strongly encouraged to adopt risk-minimizing lifestyle behaviours and are occasionally prescribed medication to treat their low bone mass. As a result, women with low bone mass are treated as though they already have a disease and require intervention by the medical system. This represents a cost not only to individuals in terms of time, but also to the health system for long term monitoring. Recent shifts in BMD monitoring reflect an easing off of surveillance as the monitoring intervals for low and moderate risk women have been increased from three to five years. It is unclear what the long term effects of this change will be, but it does suggest a reassessment of the benefit of surveillance of those at low and moderate risk.

Reconsidering risk models

While risk-based models present a useful way of conceptualizing the harm caused by disease, they also have the potential for negative outcomes in osteoporosis. The goal of the new public health was good in theory, but it focuses heavily on how individuals can manage their own health instead of looking at systemic social determinants of health. In risk-based models the social determinants of health are treated as factors that contribute to risk, rather than recognizing their role as barriers to effective prevention or management. This approach raises the potential for victim-blaming of those who cannot participate, and increases the stress placed on high risk individuals who are being told they must change their lifestyles in order to avoid becoming sick. All the while there is little focus in public health on how individuals with decreased access to resources can make these changes.

Since the goal of risk-based health promotion is to identify places in which risk can be reduced, there is a focus on modifiable factors as compared to non-modifiable factors. While this needs to be a careful balance, as providing people with options gives them a sense of control, by not officially recognizing that some risks are inherent and therefore unmodifiable again raises issues surrounding victim-blaming. Focussing on modifiable factors holds the potential for real psychological harm to those who interpret the numerous lifestyle suggestions associated with osteoporosis prevention as an indication that they caused their own disease. Similarly, there are problems with introducing models that medicalize normal, inevitable body-states, such as aging. Assigning risk categories to individuals who might simply be experiencing normal bone loss promotes increased surveillance of the population, which then blurs the lines between what is and is not a disease state. For every recorded positive outcome, there is an unknown potential for suffering of those placed in these liminal spaces of low risk, who become both sick and not sick at the same time.

What emerges from this exploration of the intersection between risk-based approaches and osteoporosis prevention is the potential for harm that is inherent in attempting to delineate risk within a population. The new public health has taken on the role of risk communicator, where it attempts to identify, define, and provide
avenues for risk mediation to individuals within a population. The goal was to contribute to public safety by reducing instances of disease, but the increased surveillance that came with this approach has had unintended and often infrequently discussed consequences. In the case of osteoporosis public health promotion is responsible for a great deal of education around prevention activities, but has also created unintended spaces for suffering in surveilled populations. Going forward, public health organizations and partners that participate in osteoporosis prevention would benefit from considering the possible negative outcomes of their approaches, rather than just the positive benefits in disease reduction, and tailor their messages and programs in ways that help to reduce these potential harmful outcomes.

References


MMSRD Recap and Winners

Authors:
Aadil Bharwani
Jennifer Asselstine

MMSRD Recap

It was our immense pleasure this year to host the 9th annual McMaster Medical Research (MMSRD), held on April 25th, 2018. Every year, MMSRD proudly showcases the tremendous efforts and achievements of McMaster University’s MD and MD-PhD students, in the hopes of encouraging students and faculty to consider the nuances of medicine by exploring research endeavours that highlight the diversity of modern healthcare. Success in improving patient care and medical practice relies upon individuals who embrace the astonishingly interdisciplinary nature of medicine to embark upon initiatives that range from examining the chemistry of novel antibiotics to efforts that affect both local and global communities.

For the first time, we were pleased to welcome students from neighbouring Canadian medical schools as part of an annual initiative that we hope will strengthen ties and foster collaborations between the next generation of physicians.

MMSRD 2018 featured an exciting program of more than 80 abstracts spanning the basic sciences, clinical research, community research, and quality improvement projects. The events of the day were highlighted by two exciting keynote speakers: Dr. Hertzel C. Gerstein, who spoke about the immense role of randomized controlled trials in the age of “big data”, and Dr. Kerstin de Wit, who spoke about the value of research in informing clinical tools and how she uses it to change her practice.

We were immensely impressed with the variety and quality of research presented by medical students, and were thrilled to provide this platform to showcase it. We hope that moving forward, MMSRD continues to grow as a platform that enables the McMaster community to gain a breadth of perspectives and find inspiration in the research efforts of peers and colleagues.
MMSRD Recap and Winners

POSTER PRESENTATIONS:

1st Place: Yung Lee
Empiric antibiotic therapy for hospital-acquired pneumonia: a network meta-analysis
Yung Lee, Yutong Fei, Romina Brignardello-Petersen, Theresa Aves, Dena Zeraatkar, Paul Alexander, Behnam Sadeghirad, Xun Li, Nathan Evaniew, Neera Bhatnagar, Isaac I Bogoch, Mark Loeb, Gordon H Guyatt, Reed A.C. Siemieniuk

ABSTRACT:

Background: Hospital-acquired pneumonia (HAP) is a common complication of hospitalisation and has a high risk of death. The optimal empiric antibiotic therapy regimen is uncertain.

Methods: We systematically searched Medline, EMBASE, and CENTRAL for randomised controlled trials (RCTs) comparing at least two empiric antibiotic regimens in patients with non-ventilator associated HAP to March 17, 2017. We performed a systematic review and network meta-analysis and network meta-regression using the GRADE framework to assess certainty.

Results: From 14,686 citations, we included 63 RCTs (10,096 patients). Most studies were limited by inadequate allocation concealment and blinding. All networks had low global heterogeneity (I² 0% to 12.9%). Fluoroquinolones reduced risk of death compared to third generation cephalosporins (relative risk and 95% credible interval; 0.46, 0.22 to 0.87, moderate certainty), fourth generation cephalosporins (0.41, 0.19 to 0.86, moderate certainty), beta-lactam/ beta lactamase inhibitors (0.45, 0.18 to 0.99, moderate certainty), and carbapenems (0.50, 0.21 to 1.03, low certainty). Fluoroquinolones also had a lower risk of treatment failure compared to most alternatives (low or moderate certainty). Second generation cephalosporins were associated with an increased risk of treatment failure compared to fluoroquinolones and other beta-lactams (moderate certainty).

Conclusion: The certainty in evidence is low or moderate for many comparisons because of imprecision and risk of bias concerns. In patients with HAP, fluoroquinolones probably reduce mortality and treatment failure compared to other commonly used options.

2nd Place: Palki Bhatt
Caregiver psychosocial wellbeing and family violence: A scoping review of factors that affect the wellbeing of children in humanitarian crisis
Palki Bhatt, Olive Wahoush

3rd Place: Anisha Dubey
Influenza A/PR8 virus infection attenuates OSM-induced Th2 immunopathology in vivo
Anisha Dubey, Fernando Botelho, Jewel Imani, Rex Park, Lillian Ho, Jann C. Ang, Yushi Yao, William Yao, Matthew Miller, Kjetil Ask, Carl D. Richards

ORAL PRESENTATIONS

1st Place: Ali Zhang
Development of broadly-protective and combinatorial antibody therapies against influenza A virus infections
Ali Zhang, Matthew S. Miller

ABSTRACT:

Background: Influenza A viruses (IAV) cause 3-5 million serious illnesses and half a million deaths each year. Vaccination is the best way to prevent infection, but protection provided is narrow and ineffective against pandemic strains due to antigenic drift in the immunodominant hemagglutinin (HA) head domain. Recently discovered broadly-neutralizing antibodies (bNAbs) that target the conserved HA stalk domain provide great promise towards development of a “universal” influenza vaccine. These bNAbs require Fc receptor binding and effector cell function to confer maximal protection. Furthermore, bNAbs have been recently shown to interact cooperatively with anti-neuraminidase (NA) antibodies.

Methods: We used antibody-dependent cell cytotoxicity (ADCC) assays and mouse models to test the potential of oseltamivir, an NA inhibitor, to cooperate with bNAbs to induce ADCC and protect against lethal IAV challenge.

Results: We demonstrate that oseltamivir causes a dose-dependent increase in bNAb-mediated ADCC of IAV infected cells. Furthermore, we found that using oseltamivir/bNAb in combination as a prophylactic is more effective than using either therapy alone in vivo.

Conclusion: The mechanism by which bNAbs protect against IAV propagation is incompletely understood. Here, we show that enzymatic inhibition of NA augments bNAb-mediated Fc-dependent effector functions. We also demonstrate that oseltamivir in combination with bNAb is more effective at preventing influenza disease progression compared to either therapy alone. Our findings may explain the variable efficacy of oseltamivir in patients, and also guide design of universal influenza vaccines and other bNAb-based anti-viral therapeutics.

2nd Place: Kevin Um
Pre-treatment with Amiodarone for Elective Electrical Cardioversion of Atrial Fibrillation: A Systematic Review and Meta-Analysis
Kevin J. Um, William F. McIntyre, Emilie P. Belley-Cote, Pablo A. Mendoza, Alex Koziarz, Guy Amit, Victor A. Chu, Richard P. Whitlock, Jeff S. Healey

3rd Place: Yosef Ellenbogen
IgG1+ B cell immunity predates IgE responses in epicutaneous sensitization to foods
Yosef Ellenbogen, Rodrigo Jiménez-Saiz, Manel Jordana

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