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MJM Volume 23, Issue No. 1, June 2026

Letter from the Editors

The McGill Journal of Medicine (MJM) is thrilled to present the latest issue of our student-run medical journal, Volume 23, Issue 1 (2026): Care Across Contexts. This issue consists of a diverse collection of clinical research, narrative reviews, case reports, educational commentary, reflections, and conference proceedings that illustrate the breadth of contemporary medicine. Together, these works highlight how healthcare professionals, researchers, and learners alike navigate complex challenges across a wide range of clinical, academic, and global settings.

The theme of this issue reflects the many environments, disciplines, and perspectives that shape modern healthcare, while emphasizing our shared commitment to improving the lives of patients and communities.

As we assembled this issue, we were reminded that meaningful advances in medicine often emerge through the exchange of ideas across specialties, disciplines, experiences, and levels of training. Whether through scientific discovery, clinical innovation, medical education, or personal reflection, each article offers a unique perspective on the evolving practice of medicine and the many contexts in which care is delivered. The contributions in this issue bring together perspectives from different students, trainees, clinicians, researchers, and educators, highlighting the importance of collaboration and mentorship in academic scholarship.

We extend our sincere gratitude to all the authors, reviewers, editors, and journal staff whose dedication and enthusiasm made this issue possible. Their commitment to advancing medical knowledge and fostering scholarly dialogue continues to strengthen the McGill Journal of Medicine's mission.

As healthcare continues to evolve in response to new discoveries, emerging challenges, and changing patient needs, it remains grounded in a common purpose: providing compassionate, evidence-informed care. We hope the articles and perspectives presented in this issue encourage continuous reflection, inspire curiosity, and foster meaningful conversations among our readers.

Thank you for joining us in this issue of the McGill Journal of Medicine. We hope you find the collection here both informative and inspiring as we explore Care Across Contexts.

Sincerely,





Alexandra Goudreau, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
PhD Candidate

Katherine Lan, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD Candidate

Foreword: Dr. Mark Basik

Why do Medical Research?

I am often asked this question: how do you split your time between clinical practice and research. I laughingly answer: 100% and 100% . So much for life balance! I am a surgical oncologist, focusing now on breast cancer surgery and the research that goes on in my lab is translational research, aiming to uncover novel approaches to overcome drug resistance, the major killer in cancer, on one hand, and to discover novel biomarkers to reduce therapy toxicity by proper selection of patients on the other. No doubt, I am prey to the same grant writing days and weeks that my fellow scientists suffer twice a year (or more these days) but I also must schedule clinics and operating days in the midst of that maelstrom. Thus I work more and, since I spend less time in the clinic and see less patients, I get paid less! So why do research as a physician?

The first answer is common to all scientists: curiosity or a passion for knowledge and understanding. This passion, and it is a passion, i.e. a deep almost relentless, bottomless desire to know, has always characterized me since my childhood. The bottom line: reality is fascinating! I tell my graduate students: when you set out to do an experiment or a study, you start with a hypothesis, which tries to answer a question. Without a question, no research! What will happen when you do the experiment or the study? An answer: either your hypothesis was correct or it was wrong! What is interesting is that both are fascinating: if it is correct, I have the feeling that a door to a part of reality has been opened and I can walk through! What I thought could be real IS REAL! There is a wonder that accompanies every answer, even if it is exactly what one expected! However, if you are wrong, then the question emerges: why? And that is even more fascinating because a door may be opening to something new, something unexpected, something you did not think about! Of course, you have to be sure that the experiment or the study is well done, and the data robust! But if it is, then this is exciting: a new adventure of knowledge is waiting for you! A wonder at the results, which are in a sense unexpected even when predicted! This is exciting!

But it all starts with a question. My original question was: why do some small tumors recur while much larger tumors do not! What is the nature of this biology? Where does the question originate from? From this curiosity as described above. Without a question, nothing happens. From a question, springs attentiveness to reality! An astrophysicist friend of mine once told a story about his daughter Sofia. They were hiking up a mountain and near the top of the mountain, Sofia, 3 years old at the time, suddenly found a strawberry, picked it up and cried out: mommy, mommy, a strawberry! The other 2 children ran up and, having verified that their little sister had quickly taken and swallowed the fruit of her discovery, started searching, quickly followed by the parents. “Another one!”, and after a while: “Look here, there are three, four...”. They quickly filled a glass of wild strawberries. On the way back, to my friend’s sincere surprise, following once again the same path down they found many more! Zero strawberries along the way up, perhaps one hundred along the way down: an effect statistically enormous. What had changed? They had changed! It is a question that leads to attentiveness, that can pick up the details and the results otherwise missed. It comes down to a passion, ignited by a question.

Now in medical research, that question is usually born from clinical experience. As we began to give chemotherapy before surgery, called “neoadjuvant chemotherapy”, and got better at it, the tumors were shrinking so well that the

pathologist could not find any trace of the tumor at surgery. This was called a pathological complete response. Some patients started asking: if the tumor is disappearing, do I really need the surgery? If there is no tumor at surgery, do I really need the radiation therapy that is routinely given when only a part of the breast is removed? These questions gave birth to 2 clinical trials, the first to determine if breast biopsies after chemotherapy could predict the absence of tumor at surgery, and so allow patients to avoid surgery. And the second to stop giving radiation to patients who had no tumor at surgery. What led to these trials? Paying attention to the patient's questions! We are still working on these trials and will know the answer in the next few years! Finally, the reason that cancer kills people is that it spreads (metastasizes) and it becomes resistant to all therapy. Although (luckily) breast cancer is not the deadliest cancer, several of my patients have died of it, and some friends as well. What can be done to prevent these deaths? This question led me to focus the lab on drug resistance, especially in the metastatic setting. Why is it that powerful drugs such as chemotherapy work less against metastatic tumors than tumors confined to the breast? What is it in the metastatic organ (liver, lung, skin, bone) that makes them more resistant? Why is the immune response poorer in the metastatic lesions than in the breast? Years ago, we started to collect biopsies from these metastatic lesions and now, we are studying them to answer these questions. We are finding that the answer may lie in the tumor stroma, and in the interaction between stromal cells, immune cells and tumor cells. I sincerely hope that we can find some clues as to why these metastatic lesions are so impervious to treatment and thus help my metastatic patients!

A non-scientist, in fact, a priest, wrote: "The more passionate one is about humanity, the more one throws oneself into research to gain something greater in knowledge that benefits humanity. But then research … becomes charity: serving humanity's path so that it may walk more easily and less painfully toward its destiny."[1]. The added motivation for medical research is ultimately love: love for our patients. What a great adventure: the wonder of understanding amplified by a love for people! So I salute the contributions in this journal. They come from various fields of medicine and from various countries. Each of them springs from an attentiveness to and a wonder before reality, like Sofia, for instance, to the consequences of prolonged drug use and to unusual manifestations of common cancers. Each of them started with a question and with a desire to improve the lot of our patients and even of medical studies in one case.

Happy reading!



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1. Giussani, L, Vivendo nella carne, Quasi Tischreden. Bioblioteca Universale Rizzoli, 1998, page 158. Google translation from the Italian.

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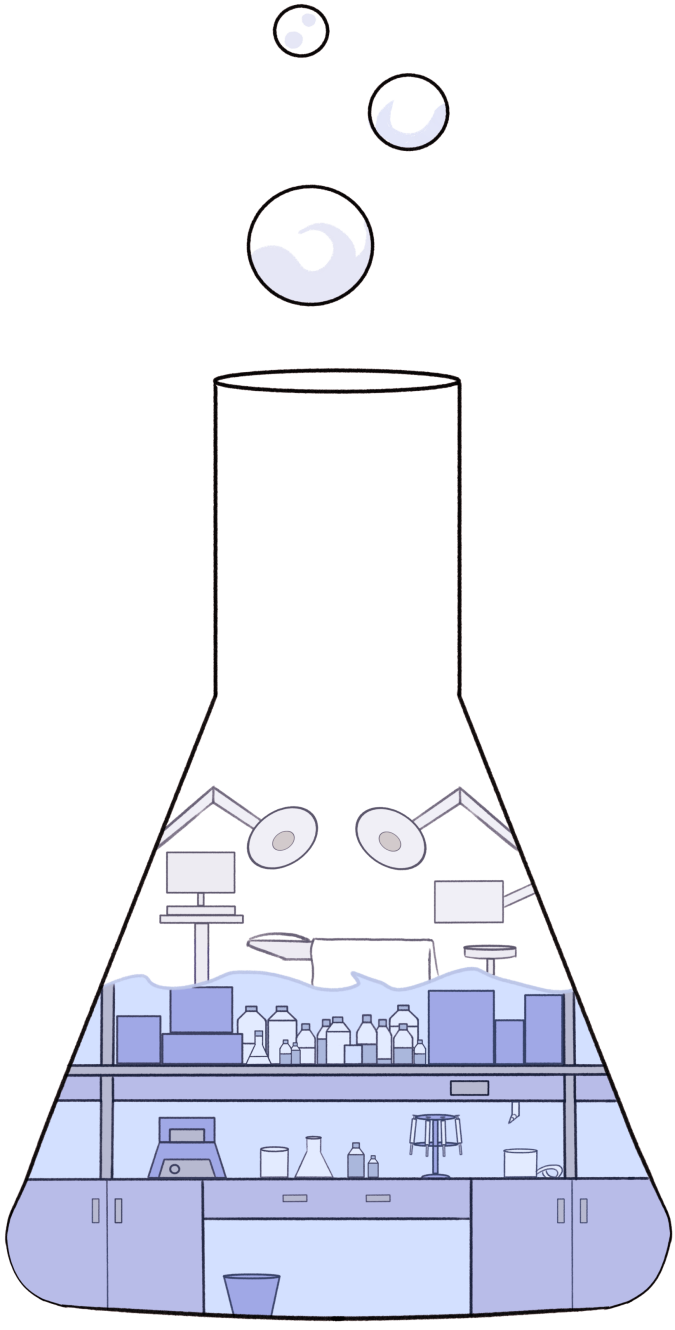
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Original Research



ORIGINAL RESEARCH
McGill Journal of Medicine

Injury-related pediatric emergency department visits during the first 2 years of the COVID-19 pandemic Department Workflow

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ABSTRACT

Objectives: To quantify the impact of COVID-19 and public health measures on pediatric injury-related Emergency Department (ED) visits during the first two years of the pandemic.

Methods: Retrospective longitudinal study assessing changes in monthly incidence of injury-related ED visits during the first two years of the COVID-19 pandemic (March 2020-February 2022) at a large Canadian tertiary pediatric hospital. Monthly fluctuations were assessed overall and by age categories (0-4, 5-11, 12-17 years). Secular time-trends and seasonality were accounted for by modelling the pre-pandemic trend using a 4-year historical control (April 2016-February 2020). We examined the impact of confinement periods (March-May 2020, October 2020-February 2021, December 2021-January 2022) on monthly fluctuations.

Results: Injury-related pediatric ED visits fell sharply at the onset of the pandemic, reaching a 45% reduction in March 2020 (Incidence Risk Ratio (IRR): 0.55; 95% CI 0.50-0.61), and peaked 30% above expected levels in January 2021 (IRR: 1.30; 95% CI 1.20-1.41). Each confinement period coincided with an initial reduction in visits, followed by a re-increase as restrictions eased. Age-specific fluctuations in injury-related ED visits varied, with no major change among 0-4-year-olds, a 56% reduction in visits at the pandemic onset among 5-11-year-olds (IRR: 0.44; 95% CI 0.37-0.54) and a 64% reduction among 12-17-year-olds (IRR: 0.36; 95% CI 0.28-0.45).

Conclusion: The consequences of COVID-19 on pediatric injury extended far beyond the first few months of the pandemic and varied according to age. Understanding how confinement influences pediatric injury may assist the development of injury prevention strategies and improve resource allocation.

KEYWORDS

COVID-19, Emergency Department, Injuries, Pediatric, Trauma

1 | INTRODUCTION

More than three years after the outbreak of COVID-19, the extent of its consequences, both direct and indirect, on the health and well-being of children and their families are still being revealed. The onset of the pandemic was associated with a marked decrease in pediatric Emergency Department (ED) utilization worldwide. (1) This has been attributed to a combination of changes in the incidence of infectious diseases such as influenza and respiratory syncytial virus infections, (2, 3) as well as changes in health-seeking behaviors. (4) A similar trend has also been observed with regards to pediatric injury-related ED visits. Specifically, Canadian studies found a 58% reduction in the total number of pediatric ED visits, and a 37-62% decrease in injury-related visits during the early pandemic period (March-May 2020) relative to the same time interval in preceding years. (5, 6)

However, it is becoming apparent that the impact of COVID-19 on pediatric ED utilization has extended beyond the early months of the pandemic. For example, pediatric ED visits in the United States declined by 51% in 2020 and remained about 22% lower than expected in 2021 and January 2022 compared to historical controls. (7) While reductions in pediatric injury in the early pandemic period have been documented in many countries, (6, 8-14) there is a paucity of data describing changes in the rates of injury-related ED presentations beyond the first 3-6 months of the pandemic. The gap in literature about longer time horizons is particularly important given that after the first wave, additional lockdown periods and school closures were implemented in many areas including in Quebec, and the peak number of daily cases of COVID-19 saw a 7.5-fold increase in December 2021 relative to April 2021. (15) This underlines the need to further evaluate changes in the incidence of pediatric injury throughout the duration of the pandemic. Additionally, the disruption of school and organized sports during the pandemic has affected children of different age groups disproportionately, which may translate into age-specific variations in ED visits for injury. (6, 7)

Therefore, this study aimed to quantify the impact of COVID-19 and associated public health measures on injury-related pediatric ED visits during the first two years of the pandemic in Montreal, Canada. We also aimed to determine if children of all ages were similarly affected and evaluate changes in the rates of hospitalization due to injury.

2 | METHODS

2.1 | Study Population

We conducted a longitudinal retrospective observational study using the electronic ED database of the Centre Hospitalier Universitaire Sainte-Justine (CHUSJ), a university-affiliated pediatric hospital in Montreal, Quebec. This database has been previously used and validated in multiple research projects. (16, 17) Patients 0-17 years old who consulted the pediatric ED of the CHUSJ between April 2016 and February 2022 and received a primary ED diagnosis related to injury were included in the study. Cases of pediatric injury were identified from a previously validated drop-down menu of 632 diagnostic criteria from the ED database (Supplementary materials). Patients who left the ED prior to being assessed by a physician were not included in the main analysis but were added in a sensitivity analysis. This study was approved by the CHUSJ Research Ethics Committee and informed consent was waived due to its retrospective and observational design.

2.2 | Outcomes and Variables

The primary outcome of interest was the change in monthly incidence of pediatric injury-related ED visits during the first two years of the COVID-19 pandemic relative to the pre-pandemic trend, overall and by age categories (preschool: 0-4 years, elementary school: 5-11 years, high school: 12-17 years). The 6-year study period was divided into the pre-pandemic period (April 2016-February 2020) and the pandemic period (March 2020-February 2022). The start of the pandemic period was defined as March 1st 2020, in keeping with the introduction of the first COVID-19-associated public

health measures in Quebec in early March 2020. (18) In a secondary analysis, we investigated seasonal changes in the risk of injury-related ED visits leading to hospitalization during the first two years of the pandemic relative to the pre-pandemic trend.

In a descriptive analysis, we investigated the incidence of COVID-19 infections and the implementation of public health measures such as lockdown periods (March-May 2020, October 2020-February 2021, and December 2021-January 2022) as potential factors associated with changes in injury-related ED visits. (18) We also compared the acuity of presentation using the Canadian Paediatric Triage and Acuity Scale (Paed-CTAS). (19) Injury diagnoses were subsequently grouped by site of injury and by type of injury using similar categories to those previously used in the literature. (9, 12) Yearly counts during the pandemic period were compared to the pre-pandemic trend.

2.3 | Statistical Analysis

Negative binomial regression with monthly indicator terms and a slope-parameter to account for any secular time-trends was used to model the monthly incidence of injury-related pediatric ED visits in the pre-pandemic trend. The change in monthly incidence during the pandemic was captured via interaction terms between the pre-pandemic and pandemic months, overall and stratified by age categories. As the catchment area of the CHUSJ was not expected to vary substantially within the months of this study, an offset parameter was not included in the model. In the secondary analysis, change in seasonal risk of hospitalization from the pediatric ED due to injury was assessed via logistic regression using seasonal indicator terms (spring=March-May, summer=June-August, fall=September-November, winter=December-February) and a slope-parameter to model the pre-pandemic trend. The analysis was aggregated by seasons due to the low monthly frequency of hospitalizations. (20) In all analyses, autocorrelation was assessed by inspection of the autocorrelated and partial autocorrelated function (ACF and PACF) plots and the Dublin Watson test. (21) Statistical analyses were performed using R statistical software version 2022.12.0+353 and all analyses were evaluated at alpha=0.05.

2.4 | Sensitivity Analysis

We identified patients who had a chief complaint related to injury at triage but left the ED prior to being assessed by a physician and, accordingly, never received a formal diagnosis of injury. As part of a sensitivity analysis, these patients were added to the patients who received a formal diagnosis of injury (included in this study) and the primary analysis investigating monthly fluctuations in injury-related ED visits was repeated.

3 | RESULTS

3.1 | Patient Characteristics

Of 458,799 pediatric ED visits during the 6-year study period, 65,364 (14.2%) were associated with injuries. There were 43,790 injury-related ED visits during the pre-pandemic period (mean 11,173 visits per year, interval March-February, standard deviation 99), compared to 10,179 and 11,395 visits in the first and second year of the pandemic, respectively. Patient and visit characteristics are summarized in Table 1. Together, children ages 0-4 and 5-11 accounted for approximately three quarters of injury-related ED visits across all periods studied. In both the pre-pandemic and pandemic periods, cranial injuries were the most common site of injury, and fractures were the most common type of injury, representing nearly 20% and 30% of injury-related ED visits, respectively (Supplementary Table 1).

3.2 | Monthly incidence of injury-related pediatric ED visits

Overall, injury-related ED visits reached a nadir in March 2020 (457 visits) and a peak in May 2021 (1,337 visits) (Figure 1). At the onset of the COVID-19 pandemic, visits fell 45% below expected levels (March 2020: Incidence Risk Ratio [IRR]: 0.55; 95% Confidence Interval

	Pre-Pandemic Period	Pandemic Year 1	Pandemic Year 2*
	Apr 2016 – Feb 2020	Mar 2020 – Feb 2021	Mar 2021 – Feb 2022
	N (%)	N (%)	N (%)
Total visits	43790	21574	11238
Visits per year	11173†	10179	11395
Age			
0–4 years	16654 (38.0)	4444 (43.7)	3916 (34.8)
5–11 years	16493 (37.7)	3809 (37.4)	4400 (39.2)
12–17 years	10643 (24.3)	1926 (18.9)	2922 (26.0)
Paed-CTAS level			
1– Resuscitation	242 (0.6)	72 (0.7)	73 (0.6)
2– Emergency	3453 (7.9)	636 (6.2)	786 (6.9)
3– Urgent	15080 (34.3)	3492 (34.3)	3856 (33.8)
4– Less Urgent	24663 (56.3)	5867 (57.6)	6569 (57.6)
5– Non-Urgent	352 (0.8)	112 (1.1)	111 (1.0)
Hospitalizations	1899 (4.3)	517 (5.1)	575 (5.0)

*Of all children who received a diagnosis of injury, 157 were missing information on age in pandemic year 2.
†Represents the mean number of visits per year interval March–February over the pre-pandemic period.
Paed-CTAS level = Paediatric Canadian Triage and Acuity Scale.

TABLE 1 Characteristics of pediatric patients and injury-related emergency department visits by period

[CI] 0.50-0.61) (Table 2). This decrease was followed by a sustained surplus in visits from December 2020 to May 2021, with visits rising 30% above expected in January 2021 (IRR: 1.30; 95% CI 1.20-1.41) and 27% above expected in April 2021 (IRR: 1.27; 95% CI 1.17-1.37), before returning to predicted levels in June 2021. Injury-related visits decreased again in September and October 2021 (September: IRR: 0.79; 95% CI 0.73-0.85, October: IRR: 0.84; 95% CI 0.78-0.91) but returned to the predicted incidence by the end of the study period.

While there was evidence of seasonality in the pre-pandemic period, with peaks between May and September (May: IRR: 1.39; 95% CI 1.32-1.46, September: IRR: 1.37; 95% CI 1.30-1.45) and a nadir in the winter months (December: IRR: 0.85; 95% CI 0.80-0.90), this seasonal pattern was not observed during most of the pandemic period (Table 2).

3.3 | Sensitivity Analysis

The sensitivity analysis included 5,415 patients who received a triage diagnosis of injury but left the ED before seeing a physician. The monthly fluctuations in injury-related ED visits of this sensitivity analysis were very similar to those of the primary analysis (Supplementary Table 2).

3.4 | Age-stratified analysis

Among the 0-4-year-olds, there was no major change from predicted counts of injury-related ED visits throughout the first two years of the pandemic (Figure 2,

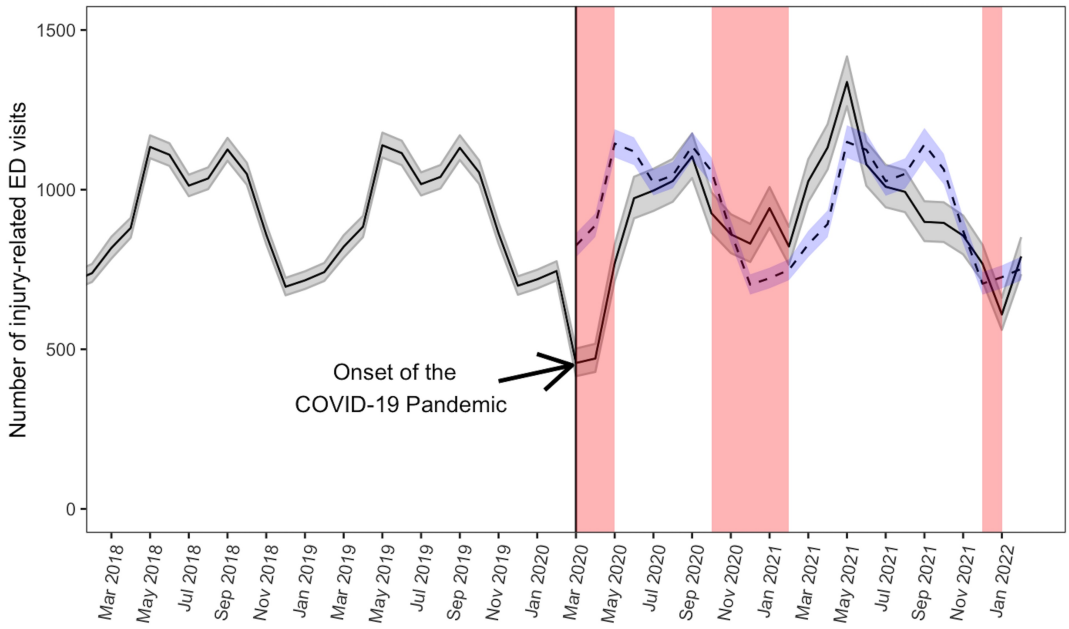


FIGURE 1 Frequency of injury-related pediatric emergency department visits and confinement periods. Solid black line: modelled trend for the pre-pandemic period (April 2016-February 2020; only February 2018-February 2020 shown for figure simplicity, as the modelled trend is identical across all pre-pandemic years) and observed incidence during the pandemic period (March 2020-February 2022); dotted black line: predicted incidence had the pandemic not occurred based on 4-year comparator period; grey region: 95% confidence interval for the fitted values; purple region: 95% confidence interval for the predicted values; pink regions: periods of confinement in Quebec (March-May 2020, October 2020-February 2021 and December 2021-January 2022). (18) ED = Emergency Department.

Table 2). In contrast, there was a 56% reduction in visits in children 5-11 years old (March 2020: IRR: 0.44; 95% CI 0.37-0.54) and a 64% reduction in children 12-17 years old (March 2020: IRR: 0.36; 95% CI 0.28-0.45) at the onset of the pandemic. While visits subsequently remained lower or similar to expected until the end of the study period in children aged 12-17 years, the monthly incidence in children aged 5-11 years reflects the patterns observed in the overall analysis.

3.5 | Risk of hospitalization

The risk of hospitalizations due to injury remained as expected at the onset of the pandemic (spring 2020: RR: 1.14; 95% CI 0.91-1.41), but increased in the summer of 2020 (+40%, RR: 1.40; 95% CI 1.10-1.77) as well as in the spring (+36%, RR: 1.36; 95% CI 1.07-1.72) and fall (+34%, RR: 1.34; 95% CI 1.08-1.66) of 2021 relative to expected risk (Supplementary Table 3, Supplementary Figure 1).

3.6 | COVID-19 cases and confinement periods

In Montreal, the daily number of new COVID-19 cases peaked in April 2020 and January 2021, before reaching an all-time high in late December 2021. (15) While injury-related ED visits decreased significantly during

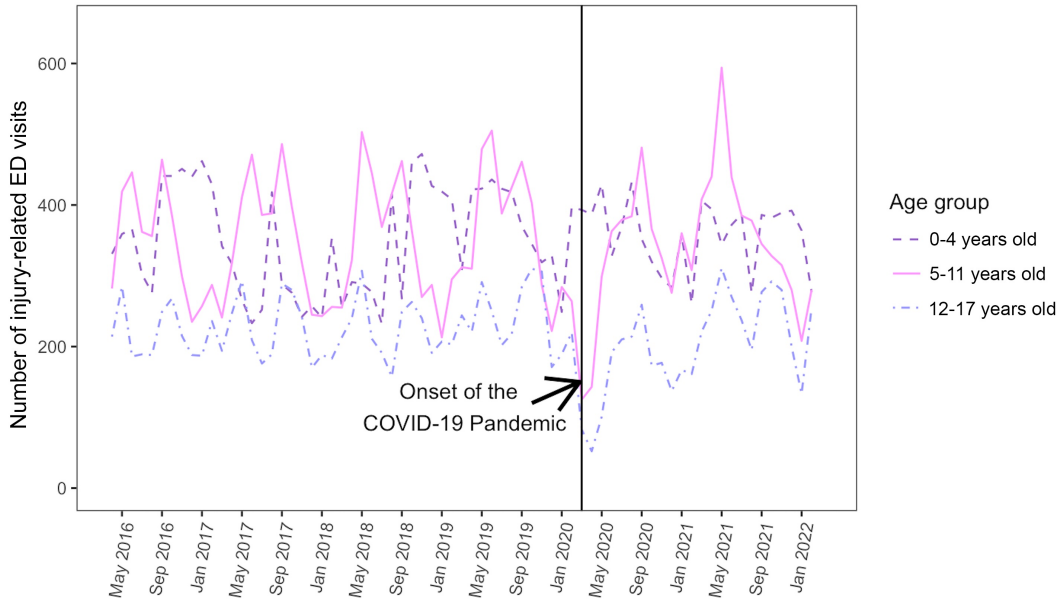


FIGURE 1 Frequency of injury-related pediatric emergency department visits by age category. ED = Emergency Department.

the first peak of COVID-19 cases in April 2020 (IRR: 0.53; 95% CI 0.48-0.59), the number of visits was higher than expected during the second peak of January 2021 (IRR: 1.30; 95% CI 1.20-1.41) and similar to expected in December 2021 (IRR: 1.09; 95% CI 0.99-1.19). We observed a reduction in injury-related ED visits at the onset of all three periods of confinement in Quebec (March-May 2020, October 2020-February 2021, and December 2021-January 2022, (18) followed by a re-increase toward the end of each confinement period or shortly after restrictions were lifted (Figure 1).

4 | DISCUSSION

This retrospective longitudinal study demonstrated that the impact of COVID-19 on pediatric injury was not uniform during the first two years of the pandemic. Indeed, important changes in injury-related ED visits occurred beyond the initial six months of the pandemic. Our results showed a 45% reduction in injury-related pediatric ED visits at the onset of the pandemic (March 2020) compared to historical controls, a finding similar to studies in the United States, (8, 9) Italy, (10, 11) France, (12) Germany, (13) and Korea. (22) However, we also found evidence of marked increases in injury-related ED visits in January 2021 (+30%) and April 2021 (+27%). Additionally, while we observed known seasonality in injury-related ED visits (with peaks in summer and troughs in winter) during the pre-pandemic period, (23), this seasonal pattern was absent in the first year of the pandemic and seemed to slowly resume by the end of the second year.

Our findings suggest that the observed changes in pediatric injury-related ED visits during the pandemic coincide less with reported incidence of COVID-19 cases and more with associated public health measures. (24) Indeed, there was a reduction in injury-related ED visits during all three periods of confinement in Quebec, followed by a rapid increase in visits as restrictions were lifted. As proposed by other groups, this observation could have been caused by minimized motor vehicle use,

	Complete model	0–4 years old	5–11 years old	12–17 years old
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
(Intercept=Mar)*	809.88 (773.75–847.36)	297.88 (243.17–367.79)	257.82 (239.17–277.35)	202.89 (186.31–220.57)
Pre-Pandemic				
April	1.08 (1.02–1.14)	1.13 (0.88–1.45)	1.15 (1.06–1.26)	1.08 (0.97–1.19)
May	1.39 (1.32–1.46)	1.11 (0.86–1.42)	1.69 (1.56–1.84)	1.37 (1.24–1.51)
June	1.36 (1.29–1.43)	1.09 (0.85–1.40)	1.74 (1.60–1.89)	0.99 (0.90–1.10)
July	1.24 (1.17–1.30)	1.00 (0.78–1.29)	1.40 (1.29–1.53)	0.88 (0.79–0.97)
August	1.26 (1.20–1.33)	1.26 (0.98–1.62)	1.47 (1.35–1.60)	0.87 (0.78–0.96)
September	1.37 (1.30–1.45)	1.13 (0.88–1.45)	1.74 (1.60–1.89)	1.23 (1.12–1.36)
October	1.28 (1.21–1.35)	1.26 (0.98–1.61)	1.44 (1.32–1.56)	1.29 (1.17–1.42)
November	1.05 (0.99–1.11)	1.23 (0.95–1.57)	1.09 (0.99–1.19)	1.15 (1.04–1.27)
December	0.85 (0.80–0.90)	1.20 (0.93–1.54)	0.91 (0.83–1.00)	0.82 (0.74–0.91)
January	0.87 (0.82–0.92)	1.13 (0.88–1.45)	0.92 (0.84–1.01)	0.88 (0.79–0.98)
February	0.90 (0.85–0.96)	1.31 (1.02–1.68)	1.01 (0.93–1.11)	0.96 (0.86–1.06)
Pandemic Year 1				
March 2020	0.55 (0.50–0.61)	1.28 (0.89–1.80)	0.44 (0.37–0.54)	0.36 (0.28–0.45)
April 2020	0.53 (0.48–0.59)	1.12 (0.77–1.65)	0.44 (0.37–0.52)	0.21 (0.15–0.27)
May 2020	0.67 (0.62–0.73)	1.26 (0.87–1.86)	0.63 (0.55–0.71)	0.32 (0.26–0.39)
June 2020	0.87 (0.80–0.94)	0.98 (0.68–1.45)	0.74 (0.65–0.83)	0.83 (0.70–0.97)
July 2020	0.98 (0.90–1.05)	1.20 (0.83–1.77)	0.95 (0.85–1.07)	1.02 (0.87–1.19)
August 2020	0.98 (0.91–1.06)	1.11 (0.77–1.64)	0.92 (0.82–1.03)	1.05 (0.89–1.22)
September 2020	0.97 (0.90–1.05)	1.01 (0.70–1.49)	0.97 (0.87–1.08)	0.89 (0.77–1.02)
October 2020	0.87 (0.81–0.95)	0.83 (0.57–1.22)	0.90 (0.79–1.01)	0.57 (0.48–0.67)
November 2020	0.99 (0.91–1.08)	0.79 (0.54–1.16)	1.05 (0.92–1.19)	0.65 (0.55–0.76)
December 2020	1.18 (1.09–1.29)	1.07 (0.73–1.53)	1.06 (0.92–1.21)	0.70 (0.58–0.84)
January 2021	1.30 (1.20–1.41)	1.03 (0.71–1.52)	1.37 (1.21–1.55)	0.80 (0.67–0.95)
February 2021	1.10 (1.01–1.19)	0.65 (0.44–0.96)	1.06 (0.93–1.21)	0.70 (0.59–0.84)
Pandemic Year 2				
March 2021	1.24 (1.14–1.34)	1.32 (0.89–1.97)	1.42 (1.25–1.61)	0.92 (0.78–1.08)
April 2021	1.27 (1.17–1.37)	1.13 (0.77–1.69)	1.32 (1.17–1.49)	0.97 (0.83–1.13)
May 2021	1.16 (1.08–1.25)	1.00 (0.68–1.50)	1.22 (1.09–1.35)	0.94 (0.82–1.08)
June 2021	0.96 (0.89–1.04)	1.11 (0.76–1.65)	0.87 (0.78–0.98)	1.12 (0.97–1.30)
July 2021	0.98 (0.91–1.06)	1.25 (0.85–1.87)	0.95 (0.84–1.07)	1.11 (0.95–1.30)
August 2021	0.95 (0.87–1.02)	0.71 (0.48–1.06)	0.88 (0.78–1.00)	0.92 (0.78–1.09)
September 2021	0.79 (0.73–0.85)	1.10 (0.75–1.65)	0.68 (0.60–0.77)	0.92 (0.80–1.06)
October 2021	0.84 (0.78–0.90)	0.98 (0.67–1.46)	0.79 (0.69–0.89)	0.93 (0.80–1.07)
November 2021	0.98 (0.90–1.07)	1.02 (0.70–1.53)	0.99 (0.87–1.14)	0.99 (0.86–1.15)
December 2021	1.09 (0.99–1.19)	1.05 (0.72–1.57)	1.05 (0.91–1.21)	0.99 (0.83–1.17)
January 2022	0.84 (0.76–0.92)	1.04 (0.70–1.55)	0.77 (0.66–0.90)	0.61 (0.50–0.74)
February 2022	1.05 (0.96–1.15)	0.68 (0.46–1.02)	0.94 (0.82–1.08)	1.08 (0.92–1.25)

*Represents the average number of injury-related emergency department visits in March of the pre-pandemic period.

Pre-pandemic period: April 2016–February 2020.

CI = Confidence interval; IRR = Incidence Rate Ratio.

TABLE 2 Changes in monthly incidence of injury-related pediatric emergency department visits during the COVID-19 pandemic, overall and by age group

fewer organized sports, and reduced time spent outside the home during lockdowns. (6, 25, 26) Similarly, the increase in injury-related ED visits shortly after confinement periods may be explained by a sudden return to sport and activities after a prolonged period of inactivity and deconditioning. (27, 28) While the described trend was preserved across all three confinement periods, there was an additional peak in injury-related ED visits in the latter half of the second lockdown period (January 2021) which was not observed in the other two lockdowns. Although the etiology of this additional peak remains unclear, it could be related to the fact that the second confinement period was the only one during which schools remained opened, or that it was substantially longer than the other two. (18) With indoor gatherings being highly restricted during the holiday period, it is also possible that families increased their participation in outdoor activities and winter sports, resulting in an increase in pediatric injuries. This would be analogous to the increase in cycling-related injuries that was noted in the literature during the summer months of the first confinement period. (6)

Our results, and those of others, established that children from distinct age groups were affected differently by the pandemic. (6, 7) While monthly injury-related ED visit rates among preschoolers (0-4 years old) remained close to predicted levels, the initial decline in visits at the start of the pandemic was greater among teenagers (12-17 years old; -64%) than among school-aged children (5-11 years old; -56%). Similarly, the decrease in injury-associated ED visits to another tertiary pediatric ED in Montreal in the early pandemic period was found to be smallest in the 2-5-year-olds and greatest in the 12-17-year-olds. (6) Changes in the incidence of injury-related ED visits among school-age children and teenagers, but not preschoolers, during the pandemic demonstrate that the associated public health measures, including lockdowns, restriction from organized sport activities, and school closures, are a major contributor to the described fluctuations in pediatric injury.

The decrease in injury-related ED visits at the onset of the pandemic has been previously attributed to caregiver avoidance of the ED and an associated reduction in presentations for minor injuries. (4) The proposed decline in presentations for minor injuries has been supported by studies demonstrating a reciprocal increase in relative injury severity in the early pandemic period, as measured by the acuity of presentation (Paed-CTAS level) and rates of hospitalization. (5, 24, 29) In contrast, we found no change from predicted in the rate of hospitalization due to injury at the onset of the pandemic (spring 2020), suggesting that the initial decrease in injury-related ED visits is unlikely to be driven by a reduction in low-acuity presentations.

The main strengths of our study include longitudinal data collection and the robustness of our findings, as exemplified by the results of our sensitivity analysis. We also evaluated changes in injury-related ED visits on a monthly rather than yearly basis, thus better delineating the impact of each period of the pandemic on pediatric injury and allowing for easier interpretation of the factors underlying these changes. Nonetheless, the single-center and administrative nature of our study has inherent limitations. Although our results reflect the experience of the largest tertiary pediatric center in Quebec, our findings may not be generalizable to other clinical settings or to other provinces where different public health measures were implemented to curtail the spread of COVID-19. In addition, injury-related ED visits are influenced by both the incidence of pediatric injury and health-seeking behaviours; however, their individual contribution cannot be disentangled. Lastly, our ability to collect detailed information on patient characteristics and types of injuries was limited by data availability and dependent upon the diagnostic criteria attributed in the ED.

5 | CONCLUSION

The impact of COVID-19 on pediatric injury extends well beyond the first few months of the pandemic. Public safety measures, including disruption of school and organized sports, appear to be associated with the observed fluctuations in pediatric injury-related ED visits. Our findings add to the growing body of evidence

demonstrating the multifaceted and long-term consequences of the pandemic and associated public health measures on the health and well-being of children. Understanding changes in the incidence of pediatric injury, both during confinement and in early de-confinement periods, may assist in the development of injury prevention strategies as well as help forecast resource needs.

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ORIGINAL RESEARCH
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Medical and Surgical Concerns in Paediatric Patients with Achondroplasia: A Retrospective Chart Review

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ABSTRACT

Background: Achondroplasia is the most common skeletal dysplasia and is associated with a wide range of medical and surgical comorbidities beyond short stature. Comprehensive descriptions of the clinical manifestations and management of these comorbidities within paediatric populations remain limited. We aimed to describe the spectrum of medical and surgical comorbidities and their management in paediatric patients with achondroplasia seen at a tertiary care centre.

Methods: We created a registry of patients seen at the Skeletal Dysplasia Clinic and conducted a retrospective cohort study of 60 patients with achondroplasia seen between January 2018 and October 2021. We collected longitudinal data on referrals, medical concerns, and medical and surgical management.

Results: Among the 60 patients included, neurological and orthopedic concerns were commonly observed. Foramen magnum stenosis/cervicomedullary compression required surgery in 37% of patients. Genu varum was treated operatively in 23% of patients. Central sleep apnea affected 25% of patients, and obstructive sleep apnea affected 62%. Fifty-three percent of patients underwent tonsillectomy/adenoidectomy surgery, and 18% received a continuous positive airway pressure (CPAP) machine. Auditory concerns were also prevalent, and myringotomy tubes were inserted in 48% of patients.

Conclusion: Paediatric patients with achondroplasia experience a broad range of medical and surgical comorbidities requiring multidisciplinary management. This study describes the spectrum of clinical manifestations and management strategies observed in a tertiary care setting and highlights the complexity of care required for this population.

KEYWORDS

Achondroplasia, Pediatrics, Disease Management

1 | INTRODUCTION

Achondroplasia is the most common skeletal dysplasia, with an estimated incidence at birth of 1 in 25,000 to 1 in 30,000. (1) Achondroplasia is typically caused by a de novo, autosomal dominant variant in the fibroblast growth factor receptor type 3 (FGFR3) gene with a glycine to arginine substitution at codon 380 (G380R), although rare exceptions to this variant occur. (1–4) The substitution in FGFR3 activates inhibitory processes that downregulate chondrocytic bone growth, (1,5) resulting in dwarfism and potential orthopedic, neurosurgical, and respiratory comorbidities. (6)

Foramen magnum stenosis in achondroplasia can result in neurologic problems (e.g., central sleep apnea) and pain, often necessitating surgical decompression. Orthopedic concerns due to metaphyseal irregularities and joint laxity may lead to orthopaedic concerns such as genu varum and pain necessitating surgical intervention. Midface hypoplasia, enlarged adenoids/tonsils, and short eustachian tubes may predispose children to respiratory infections, otitis media, and hearing loss. (7) The comorbidities associated with achondroplasia may adversely impact children's health and quality of life. (8) Management typically requires lifelong involvement from multidisciplinary healthcare providers.

The Hospital for Sick Children (SickKids) is a leading tertiary paediatric care and research centre in Canada, providing specialized care for children with rare and complex conditions (9). It cares for children with achondroplasia, including routine follow-up, treatments, and surgeries. Given the heterogenous population and complex medical needs of children with achondroplasia seen at SickKids, it is essential to systematically track their symptoms and medical intervention for clinical teams to have up-to-date information about the patient's clinical status and medical management over time. We created a site-specific registry to summarize the characteristics of children with skeletal dysplasia at SickKids to track this population's characteristics and medical and surgical management at Canada's largest children's hospitals.

1.1 | Aims

We conducted a retrospective cohort study to describe and characterize the spectrum of medical and surgical comorbidities and their management in paediatric patients with achondroplasia seen at a tertiary care centre. Specifically, the objectives of this study were to (a) describe the frequency and types of abnormalities identified through recommended achondroplasia screening and clinical assessments, and (b) summarize the medical and surgical management strategies employed for these comorbidities.

2 | METHODS

This study was approved by the Research Ethics Board (REB) at SickKids (REB# 1000059185). Given that this study used pre-existing patient data, we obtained a waiver of consent in line with institutional REB guidelines. Data were manually extracted from electronic medical records of patients seen at the Skeletal Dysplasia Clinic at SickKids between January 01, 2018, to October 31, 2021. Patient's medical records were examined for common medical concerns associated with achondroplasia, age of diagnosis or when concerns were first noted, medical and surgical management details, and effectiveness of management. Variables collected included demographic information (age, sex), genetic findings, neurological, orthopedic, respiratory, and auditory comorbidities identified through recommended screening, and associated medical and surgical management. To determine the efficacy of medical and surgical management, clinic notes were reviewed, and outcomes were categorized as resolved, partially resolved, or not resolved based on physician documentation and discussion with the research team. Data abstraction was performed by a single reviewer using a structured data collection framework developed by the research team based on study objectives and variables of interest. The framework included predefined fields for demographic characteristics, genetic findings, and clinical comorbidities (neurological, orthopedic, respiratory, and auditory), as well as associated medical and surgical management and outcomes. Management outcomes were recorded as documented in the electronic medical record by treat-

ing clinicians, without independent adjudication. For patients with multiple clinical concerns, outcomes were abstracted separately for each condition. Duration of symptoms and time to resolution were not consistently documented and therefore were not systematically analyzed. Body mass index (BMI) was calculated based on patients' most recent height and weight. Demographic variables collected included age and sex. Additional sociodemographic information was not consistently available in the medical records and was therefore not included in the analysis.

Data from patient charts were manually recorded into standard surveys on REDCap Internal (REDcap 12.3.3 - © 2022 Vanderbilt University). Data were processed using the Excel® software (Microsoft Corp. 2016) and analyzed using descriptive statistics. All percentages are reported as a percent of the total number of patients in the study (n = 60), unless stated otherwise. When reporting non-mutually exclusive subgroup indications, absolute numbers are presented without percentages to avoid misleading denominators.

3 | RESULTS

Sixty patients with achondroplasia were included in this study. The median age at the time of data collection was 10.1 years (range: 2.8-23.5 years). Thirty-one patients were male (52%) and 29 were female (48%).

Seven patients (12%) had inherited FGFR3 mutations. Fifty-two patients (87%) had a typical de novo mutation. One patient (2%) had an abnormal FGFR3 variant (de novo, c.835A>T, p.Ser279Cys). All patients had genetic testing. The most common comorbidities were foramen magnum stenosis, kyphosis, and recurrent otitis media. Findings are summarized in Table 1. Patients could have multiple comorbidities and therefore may be represented in more than one diagnostic category.

3.1 | Medical and Surgical Concerns and Management

3.1.1 | BMI and Gross Motor Development

Fourteen patients (24%) were considered overweight or obese. One patient in the obese category was seen by dietetic nutrition for weight management. One additional obese patient was enrolled in an obesity management program.

The age at which the patients were first noted to sit independently and began walking was recorded as a guide for gross motor development. The age the child first started sitting was reported for 12 children. The median age was ten months (range: 8-15 months). The age when the child first started to walk was reported for 35 children. The median age was 20 months (range: 12-36 months).

3.1.2 | Neurological Concerns

Forty-five patients (75%) had foramen magnum stenosis, and 27 (45%) had cervicomedullary compression. All 22 patients (37%) who underwent cervicomedullary decompression surgery showed significant narrowing of the foramen magnum.

Following initial cervicomedullary decompression surgery, neurological concerns were fully resolved without the need for revision surgery in 15 patients. Symptoms were partially resolved in six patients who required revision surgery due to bony regrowth or recurrent or worsening symptoms. Among these six patients, symptoms were fully resolved after revision surgery in three patients. One patient experienced persistent symptom progression after the first revision but achieved full resolution following a second revision surgery. One patient had radiographic evidence of bony regrowth but remained asymptomatic and did not require further surgical intervention. One patient experienced chronic back and neck pain that did not resolve following revision surgery. Outcome data were not documented for one patient.

Seven patients underwent cervicomedullary decompression surgery for symptoms related to sleep apnea. Sleep apnea symptoms were fully resolved for three patients, partially resolved in one patient following two revision surgeries, and not resolved in three patients. For the patients whose sleep apnea symptoms did not resolve following surgical intervention, additional information regarding comorbidities or subsequent management was not available at the time of manuscript preparation.

Medical concern	Patient Count (percentage), n = 60	Median Age (min–max, years)
BMI		
Underweight (BMI < 18.5)	3 (5%)	6 (5–14)
Normal weight (BMI 18.5–25)	43 (72%)	8 (2–23)
Overweight (BMI 25–30)	7 (12%)	12 (5–18)
Obese (BMI > 30)	7 (12%)	17 (15–20)
Neurological complications		
Foramen magnum stenosis	45 (75%)	1.0 (0.0–16)
Cervicomedullary compression	27 (45%)	1.1 (0.3–11)
Cervicomedullary decompression surgery	22 (37%)	1.3 (0.4–12)
Cervicomedullary decompression revision surgery	6 (10%)	6.0 (0.5–18)
Second cervicomedullary decompression revision surgery	1 (2%)	2.2
Orthopedic complications: kyphosis		
Kyphosis Notes	38 (63%)	1.3 (0.8–11)*
Resolved spontaneously / No intervention required	37 (62%)	N/A
Intervention required	1 (2%)	11
Orthopedic complications: Genu Varum		
Genu varum requiring correction	14 (23%)	10 (6–17)
Guided growth	11 (18%)	10 (6–15)
Osteotomy	2 (3%)	16.5 (16–17)
Limb lengthening	1 (2%)	9
Respiratory complications		
Central sleep apnea	15 (25%)	1.1 (0.3–5)†
Obstructive sleep apnea	37 (62%)	1.6 (0.1–14)‡
Tonsillectomy/Adenoidectomy	32 (53%)	2.8 (0.8–9)§
Continuous positive airway pressure (CPAP)	11 (18%)	3.3 (0.7–13)
Auditory complications		
Recurrent otitis media	31 (52%)	2.0 (0.7–7)‖
Middle ear effusions	22 (37%)	1.6 (0.2–7)¶
Hearing loss	23 (38%)	3.0 (0.2–15)**
Myringotomy tubes	29 (48%)	2.3 (0.7–10)††

Note:

*Age of kyphosis was not specified for 10 patients.

†Age of CSA diagnosis was not specified for 1 patient.

‡Age of OSA diagnosis was not specified for 2 patients.

§Age of T/A was not specified for 1 patient.

‖Age first diagnosed was not specified for 7 patients.

¶Age first diagnosed was not specified for 2 patients.

**Age first diagnosed was not specified for 1 patient.

††Age of first tube insertion was not specified for 2 patients.

TABLE 1 Summary of medical complications of achondroplasia patients

In addition to sleep apnea, one patient underwent cervicomedullary decompression surgery for papilledema edema, urinary incontinence, sudden loss of consciousness and balance, and headaches, and two for myelopathy. All these concerns were fully resolved post-operatively. One patient experiencing severe developmental delays demonstrated no improvement post-operatively. One patient underwent cervicomedullary decompression surgery for chronic neck and back pain. These symptoms partially resolved initially but recurred one month post-operatively.

3.1.3 | Orthopedic Concerns

Thirty-eight patients (63%) had thoracolumbar kyphosis. In nearly all (37/38) cases, the kyphosis resolved without intervention as the patient aged and gained strength. In one patient, kyphosis was associated with symptoms of neurogenic claudication at 11 years of age; symptoms were not resolved at the time of data collection and corrective surgery was pending.

Fourteen patients (23%) had genu varum requiring surgical correction. Surgical correction resulted in com-

plete resolution of genu varum in 12 patients. In one patient, genu varum partially resolved following initial guided growth surgery, but subsequently recurred and was fully corrected after a second guided growth procedure. For one patient, the deformity was not adequately resolved with guided growth; therefore, an osteotomy was performed which fully corrected the genu varum.

3.1.4 | Respiratory Concerns

Fifteen patients (25%) had central sleep apnea, and 37 patients (62%) had obstructive sleep apnea. Among patients who underwent tonsillectomy/adenoidectomy, symptoms were fully resolved in 14 patients, partially resolved in seven patients, and not resolved in five patients. Outcome data following tonsillectomy/adenoidectomy were not documented for six patients.

Eleven patients (18%) were prescribed continuous positive airway pressure (CPAP) therapy. CPAP therapy resulted in complete resolution of symptoms in five patients, partial resolution in three patients, and no resolution in three patients.

3.1.5 | Auditory Concerns

Thirty-one patients (52%) experienced recurrent otitis media, 22 patients (37%) had middle ear effusions, and 23 patients (38%) had transient hearing loss. Twenty-nine patients (48%) underwent myringotomy tube placement. Indications for surgery included recurrent otitis media (22 patients), middle ear effusions (18 patients), hearing loss (14 patients), speech delay (seven patients), and nasal congestion (one patient); some patients had more than one indication. The indication for surgery was not specified for four patients.

Following myringotomy tube placement, symptoms were fully resolved in 13 patients, partially resolved in nine patients, and not resolved in two patients. Outcome data were not documented for five patients.

3.2 | Specialty Referrals

The most common specialty referrals included respirology (92%) for a sleep study; neurosurgery (75%) for foramen magnum stenosis; ENT (75%) for a tonsillectomy/adenoidectomy which is commonly used as a treatment for obstructive sleep apnea; and orthopaedic surgery (67%) which is most commonly for an assessment of limb alignment. A complete list of specialties and referrals and the reasons underlying the referrals are summarized in supplementary Table S1.

4 | DISCUSSION

This retrospective study summarizes the clinical characteristics of children with achondroplasia who were evaluated within four years at SickKids to better understand the prevalence and management of achondroplasia-related comorbidities and concerns within the Canadian paediatric population. Fifty-two patients (87%) had a typical de novo mutation, keeping with a previously reported value of 80%. (10)

Concerning development, 50% of children with achondroplasia are reported to sit independently at nine months, (11) and the median age of walking independently in children with achondroplasia is 21.2 months. (12) We observed similar findings with an average age of sitting at 10 months and an average age of walking at 20 months. In our cohort, gross motor development milestones were available for only a subset of patients, with age at first sitting documented for approximately 20% and age at first walking for 58%. As a result, these findings should be interpreted cautiously and primarily as descriptive observations rather than representative estimates for the entire cohort. Gross motor delays are expected in children with achondroplasia due to biomechanical differences. Accordingly, achondroplasia-specific developmental charts should be used when assessing these patients. (12)

Excess weight is a significant risk factor for individuals with achondroplasia as it can exacerbate comorbidities such as obstructive sleep apnea, genu varum, spinal stenosis and increase mortality. (13) Twenty-four percent of our patients fell within the overweight or obese BMI category. Currently, no established standards exist to evaluate, prevent, or treat obesity in individuals with achondroplasia. (14) However, most patients in our study were counselled on healthy eating and exercise, whereas two were referred to nutrition/dietetics or obesity management. These findings suggest that

structured programs or recommendations may benefit children with achondroplasia who require weight management support. Overweight and obesity were more common in older patients in this cross-sectional study, suggesting that the study design may underestimate the true lifetime risk.

Neurological comorbidities were common in our study population, and 37% of the patients underwent cervicomedullary decompression surgery. This finding is higher than what has previously been reported (3-26%), (15,16) and may be attributed to the fact that SickKids is a tertiary care center with a large neurosurgery department. The foramen magnum is small in children with achondroplasia, which can compress the brain stem and upper cervical spinal cord, potentially resulting in myelopathy, apnea, and sudden death. (17–19) Cervicomedullary decompression surgery may result in postoperatively complications such as cerebrospinal fluid leaks, although it has been found to provide significant clinical benefits in the context of achondroplasia. (20) Consistent with the literature, most of the patients in our study showed significant improvement post-surgery. No patients showed deterioration of symptoms or significant complications due to surgery.

Common orthopaedic concerns include thoracolumbar kyphosis (typically with an apex at the second lumbar vertebra) and genu varum. Thoracolumbar kyphosis usually resolves spontaneously as infants' muscle tone improves with age. (21) If the kyphosis does not resolve spontaneously, spine bracing may prevent progression, although its effectiveness is not proven. (21) A minority of paediatric patients may be considered for lumbar spinal surgery, particularly if there is a concomitant neurogenic claudication. (21) While 63% of patients in our study experienced kyphosis, only one patient (2%) required surgical correction. Joint hypermobility in the coronal plane of the knee is commonly observed in achondroplasia. This can exacerbate genu varum, initially caused by altered tibial shape. (22) It has been reported that approximately 10% of children have significant genu varum by age five, which increases to approximately 40% during adulthood. (23) This situation can lead to lateral knee pain and gait disruptions, including a 'lateral thrust' when standing. Similarly, 23% of patients had genu varum that required surgical correction (guided growth, osteotomy, or limb lengthening). Surgical intervention was effective in reducing genu varum in our patient population. It is important to regularly assess for genu varum in patients with achondroplasia and consider surgical correction when patients have significant malalignment or asymptomatic malalignment before completing skeletal maturity. (24,25)

Approximately half of the patients (52%) in our study had episodes of recurrent otitis media, consistent with previous reports indicating that nearly 60% of patients experience at least one episode in the first year of life. (23) Conductive hearing loss has previously been reported in 38% of individuals with achondroplasia by adulthood. (23) We found that 38% of patients in our study showed evidence of transient conductive hearing loss. Auditory comorbidities may cause speech delays and articulation concerns. Of significance, myringotomy tube placement is effective in addressing these concerns. (26)

Sleep apnea is the most common respiratory problem in individuals with achondroplasia due to adenotonsillar hypertrophy or upper airway obstruction. (27) It has been reported that 25% of children with achondroplasia undergo tonsillectomy/adenoidectomy by eight years old and almost 40% by adulthood. (26) In the current study, 53% of patients underwent tonsillectomy/adenoidectomy. Reports of tonsillectomy/adenoidectomy effectiveness in treating obstructive sleep apnea have been mixed. One study reported that 60% of children treated with tonsillectomy/adenoidectomy required ongoing CPAP therapy to manage symptoms. (28) In contrast, another study reported that 64% of patients had complete resolution of obstructive sleep apnea symptoms after tonsillectomy/adenoidectomy and required no additional management. (29) We have observed that obstructive sleep apnea concerns were fully resolved following tonsillectomy/adenoidectomy in 38% of patients. Our findings highlight the need for ongoing monitoring and management of sleep apnea in this population, as some patients may require additional interventions to control obstruc-

tive sleep apnea fully.

4.1 | Strengths, Limitations, and Future Directions

While registries and natural history studies exist for achondroplasia, they are geographically limited to the United States, Europe, and India. (4,30,31) This study is the first to summarize the clinical findings of achondroplasia concerns and management within a Canadian paediatric population. This study also revealed the diverse and interrelated nature of medical concerns associated with achondroplasia which extend beyond stature and can cause significant morbidity. Pharmacological treatments for achondroplasia primarily focus on height and growth-related outcomes. (32) We recommend broadening the focus to also account for the concerns discussed above. Additionally, developing standardized methods to monitor and manage weight in children with achondroplasia may help to mitigate other serious comorbidities. Musculoskeletal pain, spinal pathology, and lower limb deformities may limit the feasibility of exercise-based weight management strategies in some patients with achondroplasia, underscoring the need for individualized, multidisciplinary approaches.

A limitation of this study is that there was limited availability of data on certain treatments and outcomes due to inconsistencies in reporting within patient charts, leading to potential gaps in the information collected. Our study offers valuable insight into the medical comorbidities and concerns of achondroplasia at SickKids, but its application may be limited as it only includes patients from a tertiary referral centre. Patients with fewer concerns may be less likely to attend referral centres, meaning estimates of medical event rates are likely higher from referral centre studies than from population-based studies. Individual variability in outcomes may be influenced by factors such as age, BMI, and baseline disease severity, which could not be systematically explored in this retrospective cohort.

As a retrospective chart review, outcome assessment relied on the accuracy and completeness of clinical documentation, which may introduce documentation or recall bias. Additionally, the duration of symptoms and time to resolution could not be systematically evaluated due to inconsistent reporting. Distinguishing manifestations directly attributable to achondroplasia from those influenced by multifactorial contributors is challenging in retrospective studies and underscores the importance of cautious interpretation.

While most patients in our cohort harbored the typical de novo FGFR3 p.G380R variant, a small subset had inherited or atypical variants. Although genotype–phenotype correlations have been proposed in achondroplasia, the limited number of patients with non-classical variants in this cohort precluded meaningful subgroup analyses. Future multicenter registries with larger sample sizes may help elucidate whether specific genetic variants are associated with differential risks of particular clinical comorbidities and inform more personalized management strategies.

5 | CONCLUSION

This registry-based retrospective cohort study primarily aimed to characterize the range of medical and surgical concerns and their management in children with achondroplasia, rather than to evaluate the effectiveness of a registry itself. Our study highlights the need for various forms of medical and surgical management for children with achondroplasia by a multidisciplinary team. Healthcare providers must be aware of these concerns, as early detection of comorbidities can be critical for optimal clinical outcomes. By improving our understanding of the clinical presentations involved in achondroplasia and what constitutes effective management, we can provide personalized care for this population of patients and improve their quality of life.

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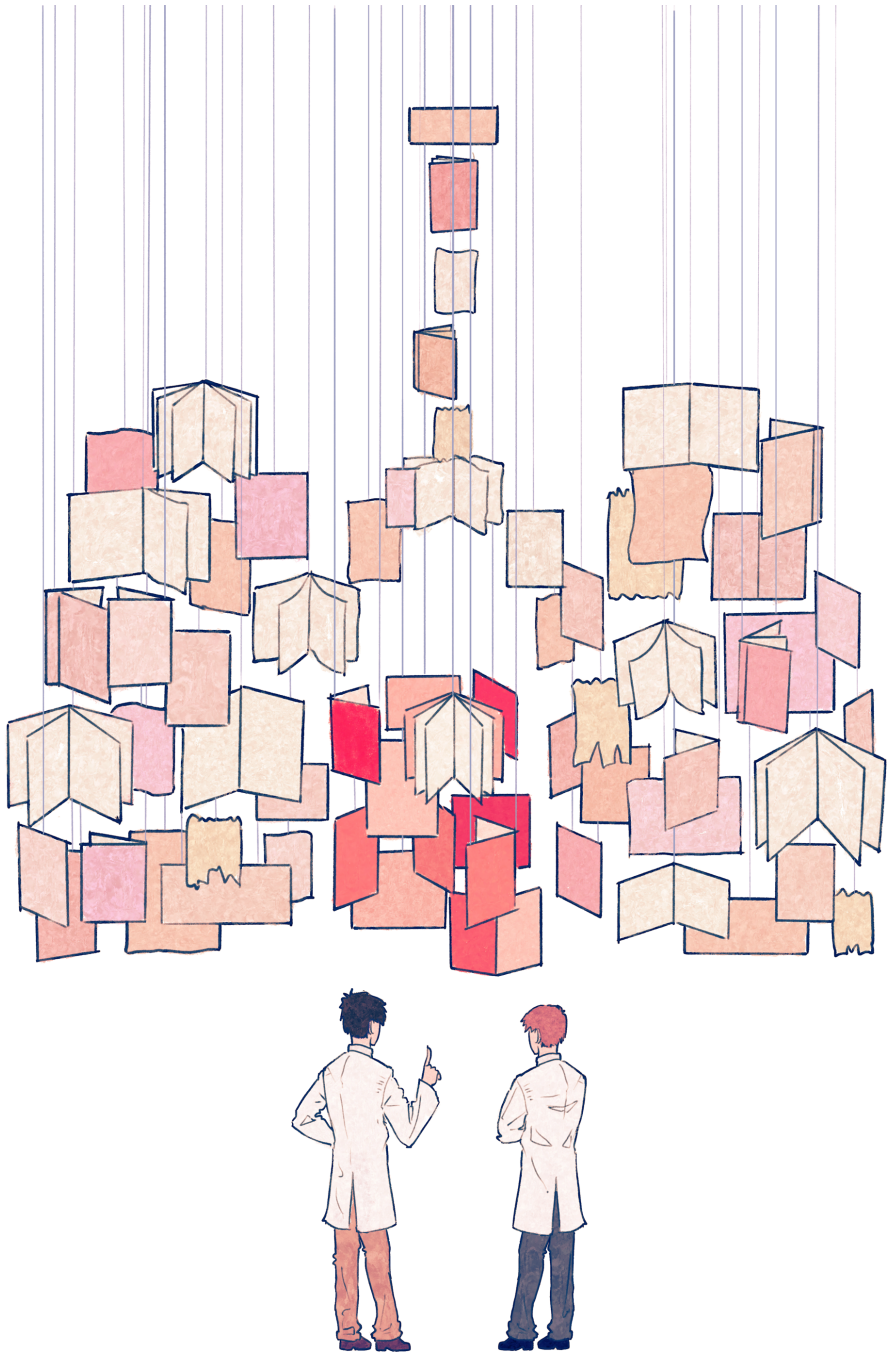
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Narrative Review



NARRATIVE REVIEW
McGill Journal of Medicine

Cardiac Involvement in Melanoma: A Review of Clinical Manifestations and Management Strategies

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ABSTRACT

Cardiac involvement in melanoma, while clinically uncommon, presents significant diagnostic and therapeutic challenges due to its often silent course and nonspecific manifestations. Melanoma, a highly metastatic skin cancer, can spread to the heart, often remaining asymptomatic until advanced stages, when it may cause nonspecific symptoms such as chest pain and arrhythmias. This review explores the epidemiology, pathophysiology, and clinical manifestations of melanoma-related cardiac metastases, emphasizing the importance of advanced imaging techniques for early detection. It also discusses current management strategies, including immunotherapy and targeted therapies, which have improved survival outcomes. However, despite these advances, the prognosis for patients with cardiac metastases remains poor, highlighting the need for further research into more effective treatments.

KEYWORDS
Melanoma, Cardiac metastases

1 | INTRODUCTION

The skin, derived from the neuroectoderm and mesoderm, is the human body's largest organ and is where cancer can arise from all three layers (i.e., epidermis, dermis, and hypodermis). Indeed, exposure to ultraviolet radiation and a variety of environmental carcinogens can lead to genetic damage and increases the risk of skin cancer (both melanoma and nonmelanoma). Melanoma is the more aggressive and lethal type of skin cancer because of the increased likelihood for metastasis. (1) Despite extensive investigations into cutaneous manifestations and distant organ metastases, the cardiac implications of malignant melanoma have received relatively limited attention and remain largely uncharted. Furthermore, the incidence of malignant melanoma con-

tinues to rise. (1) While the skin, brain, liver, bone, and intestine are the primary locations of distant metastases in melanoma, it may also affect the heart and present in various ways. (2,3) Secondary cardiac metastases are more common than primary cardiac tumours. (4) Several imaging techniques are crucial in promptly identifying and characterizing heart metastases. Managing these cardiac manifestations often requires surgical procedures or systemic treatments, marking a significant advancement in caring for advanced melanoma patients.

Understanding how melanoma involves the heart is critical for timely diagnosis and appropriate management. Cardiac metastases in melanoma are associated with worse survival, yet they are frequently missed during life and are most often identified only at autopsy. In a review by Tyebally et al. (2020), patients with cardiac metastases demonstrated markedly higher two-year mortality rates compared to those without cardiac involvement (59% vs. 37%; p = 0.034), with a median survival of 1.2 years versus 4.4 years, respectively. (5) Management may also differ when cardiac metastases are diagnosed antemortem since treatment must address both the primary malignancy and symptoms arising from cardiac involvement. In one study, 48% of patients experienced at least one cardiovascular complication within the first year following diagnosis of metastatic melanoma. Treatment strategies for cardiac metastases may include immunotherapy (65%), targeted therapy (35%), radiation therapy (25%), and, in some cases, surgical intervention (15%). (6) This review outlines the epidemiology, presentation, imaging techniques, histopathology, and surgical and medical treatments for melanoma that has spread to the heart. While imaging modalities and treatments rapidly evolve, this article aims to provide an updated review.

2 | EPIDEMIOLOGY

The incidence of malignant melanoma has been steadily rising in developed countries over the past few decades, with an estimated 77 230 new cases and over 8 000 deaths in the United States in 2020 alone. (7) In Canada, an estimated 11 300 new cases of melanoma were reported in 2024, with 1 300 deaths—a 17% increase from 2023. Ultraviolet (UV) radiation remains the primary risk factor, accounting for approximately 85% of melanomas in Canadians over age 30. (8) Although the incidence continues to rise, survival rates in the United States have increased significantly in the past decade, which can be attributed to the development of new targeted immunotherapies. (7) While the 5-year survival rate for patients diagnosed with stage I or II melanoma exceeds 99%, those presenting with distant metastases at diagnosis have a much lower 5-year survival, currently estimated at approximately 35%. (9, 10) Among various malignancies, malignant melanoma has the highest rate of metastasis to the heart. (11) In an autopsy series of 70 patients with metastatic malignant melanoma, cardiac involvement was seen in 64% of patients. (12) Within the group of 70 patients, only 16% had clinically significant cardiac dysfunction while alive. A malignant tumour in the heart did not lead to dysfunction unless there was considerable involvement. (12) Additionally, metastases to the heart may be undetected for over 20 years after the primary cutaneous melanoma diagnosis and excision. (13) Although predating the widespread use of immunotherapy, one study demonstrated that 23% of patients survive beyond six months following the diagnosis of any metastatic cardiac lesion. (5)

3 | PATHOPHYSIOLOGY

Melanoma is a type of cancer originating from pigment-producing cells called melanocytes, which undergo malignant transformation. As melanocytes are produced from neural crest-derived cells, melanomas, although primarily found in the basal layer of the epidermis, can develop and migrate elsewhere including the heart. (14) The pathology of cardiac melanoma remains challenging due to its rarity and the complex nature of the disease. In general, malignant tumours can reach the heart via four main routes: hematogenous spread, lymphatic dissemination, transvenous extension, or direct invasion from adjacent structures such as the lungs or mediastinum. In the case of melanoma, hematogenous

spread predominates, allowing circulating tumour cells to enter the bloodstream and seed distant organs, including the heart. (15) Once in circulation, melanoma cells can adhere to the endothelium and infiltrate cardiac tissue. This mechanism enables tumour cells to lodge within the myocardium or endocardium, sometimes resulting in intracavitary masses. (16) Cardiac metastases from melanoma can involve all three layers of the heart wall and are most frequently observed in the pericardium (69.4%), followed by the epicardium (34.2%), myocardium (31.8%), and endocardium (5%). (17) Moreover, the right atrium is the most common location for melanoma-originating cardiac metastases, and intracavitary tumours are thought to occur via metastasis through the inferior vena cava. Metastases to the left side of the heart are thought to be associated with pulmonary embolism due to the pulmonary circulation and the increased vascularization and mass of the left myocardium. (6) Additionally, metastasis to the valves rarely occurs. (11)

4 | CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

Cardiac metastases often remain asymptomatic until they grow large enough to physically interfere with heart function, causing what is known as a mass effect. Patients may initially experience nonspecific signs and symptoms, including but not limited to chest pain, palpitations, dyspnea, pericardial effusion, superior vena cava syndrome, dysrhythmias, congestive heart failure, and right ventricular outflow and inflow obstruction. (6, 11) However, in many instances, clinical features such as tachycardia, dyspnea, and anasarca are attributed to non-cardiac involvement of metastatic melanoma, which is explained by the fact that most of the cardiac metastases are relatively small. Cardiac function is only impaired in approximately 30% of patients with cardiac metastases. (4) The nonspecific nature of cardiac metastases and their relatively small size pose a significant challenge for early diagnosis and are often only found at autopsy. Indeed, greater than 50% of patients with metastatic melanoma will have cardiac involvement as proven postmortem. (6) Detection and diagnosis prior to death occur in less than 2% of patients. (6) For all the above reasons, non-invasive imaging techniques play a pivotal role in the early detection of cardiac involvement. Electrocardiography (ECG), however, remains a limited diagnostic tool for identifying cardiac metastases from melanoma due to its nonspecific findings. (11) While ECG changes may occasionally be the first indication of cardiac involvement, most alterations are not unique to cardiac tumours. These abnormalities can result from tumour infiltration, pericardial effusion, or coexisting cardiac conditions, making it difficult to distinguish metastatic involvement based solely on ECG. As highlighted in studies by Hanfling (1960) and Harvey (1968), there are no pathognomonic ECG patterns for cardiac metastases, underscoring the need for more specific imaging modalities for accurate diagnosis. (18, 19) Magnetic resonance imaging (MRI) and computed tomography (CT) have proven to be eligible diagnostic imaging tools as they offer a larger scan size, allowing for full analysis of the chest and identification of any metastases. Furthermore, imaging lung tissue pleura and blood vessels surrounding or entering the heart is important in identifying any metastases invading the heart. While both MRI and CT offer an adequate field of view, contrast resolution and signal intensities in MRI are helpful in differentiating between healthy tissue and cancerous tissue by their characteristic brightness on T1-weighted images. (4)

Regarding histological diagnosis, ultrasound-guided transvenous biopsy is a safe and adequate method of obtaining tissue for diagnostic study compared to a thoracotomy. (14) Histopathological examination reveals distinctive features that include melanin granules, epithelioid or spindle-shaped cells, and the expression of melanoma-associated markers (e.g., S100 and Melan-A). (20) Furthermore, cytological examination of pericardial fluids may also be done, but it was shown to be non-diagnostic in many instances, with only 44-65% of suspected malignant pericardial effusions. (21) Differentiating primary cardiac tumours metastases from and metastases from other primary cancers is of utmost impor-

Disease presentation	Treatment Options
Asymptomatic, solitary lesion	Surgery if complete resection possible
Multiple lesions/systemic disease	Immunotherapy (PD-1/CTLA-4) and/or targeted therapy (BRAF+)
Non-severe symptomatic, BRAF+	Targeted therapy to reduce tumour size, possible surgery later
Severe symptoms, unstable	Urgent surgical resection if feasible
Pericardial effusion	Pericardial drainage if feasible
Chemotherapy	Not first-line and for refractory cases only

TABLE 1 Cardiac Involvement in Melanoma Treatment

tance and requires the expertise of a skilled pathologist.

5 | MANAGEMENT

Management of cardiac manifestations in malignant melanoma necessitates a multidisciplinary approach. The specific intervention depends on several factors, including the location and extent of cardiac involvement, the patient's comorbidities and performance status, and the molecular characteristics of the melanoma. Surgical interventions, such as excision of cardiac metastases or pericardial drainage, may be considered in select cases. (7) The management of cardiac metastatic melanoma should be tailored to each patient's clinical and tumour characteristics. In asymptomatic individuals with a solitary cardiac metastasis, surgery may be a reasonable first-line option if complete resection with clear margins is feasible and would result in no residual disease. Surgical excision is often prioritized when the tumour causes significant hemodynamic compromise. For patients experiencing hemodynamic instability, urgent surgical resection with margins of healthy tissue is recommended, provided the patient's overall condition permits. (22) However, in most cases, cardiac metastasis occurs in the context of widespread metastatic melanoma, which limits the feasibility and curative potential of surgery. As such, surgery is rarely curative but may still be offered to alleviate mass effect or prevent cardiovascular complications, particularly in patients with limited systemic involvement or indolent disease progression. In these cases, surgery is often used in conjunction with systemic therapy or delayed as part of a salvage approach once disease burden is reduced (Table 1). (23)

Indeed, the advent of **immunotherapy and targeted therapy** has revolutionized the management of advanced melanoma, leading to a dramatic improvement in 5-year survival rates compared with conventional chemotherapy. (24) Consequently, chemotherapy is generally no longer used as first-line treatment in metastatic melanoma. Just ten years ago, metastatic melanoma was almost universally lethal, with an overall 5-year survival rate of approximately 5%. According to the American Cancer Society, the current 5-year survival rate for metastatic melanoma is approximately 35%, reflecting significant improvements. (10) Recent advances in targeted therapies suggest that all patients with metastatic melanoma should be evaluated for BRAF and MEK mutations, especially given that BRAF genes are found in half of melanoma cases, and that anti-BRAF and anti-MEK therapies, such as vemurafenib and cobimetinib, can be offered to patients with improved response. (25) Vemurafenib, a selective BRAF inhibitor, was shown to have a positive response in over 60% of patients with metastatic melanoma as demonstrated by regression in tumour size, survival benefits, and better response time compared to chemotherapy agents such as dacarbazine. (26) Furthermore, immune checkpoint blockade such as PD-1 blocking antibodies (i.e., nivolumab/pembrolizumab) as well as CTLA-4

Stage	Main Treatment Options
Stage 0	• Surgery
Stage I	• Surgery with or without Lymph Node Mapping/Biopsy
Stage II	• Surgery with or without Lymph Node Mapping/Biopsy, Adjuvant Immunotherapy (e.g., pembrolizumab)
Stage III (resectable)	• Surgery • Adjuvant Immunotherapy (nivolumab, pembrolizumab) • Targeted Therapy if BRAF/MEK+
Stage III (unresectable)	• Immunotherapy • Targeted Therapy (if BRAF/MEK+) • Radiation • Chemotherapy (rare)
Stage IV	• Immunotherapy (PD-1: nivolumab/pembrolizumab, CTLA-4: ipilimumab) • Targeted Therapy (BRAF/MEK+) • Radiation or Surgery (palliative)
Recurrent	• *Similar to Stage IV: systemic therapy preferred* • May include surgery for symptom relief

TABLE 2 Overview of Melanoma Treatments

blocking antibodies (i.e., ipilimumab) have shown significantly improved survival and durable responses in patients with advanced melanoma (Table 2). (27,28)

6 | CONCLUSION

Cardiac metastases originating from melanoma are under-researched, and treatment options remain underdeveloped. Melanoma is a major cause of cardiac metastases. Cardiac metastases from melanoma can be found in all three layers of the heart, whereas non-melanoma cardiac metastases tend to affect the pericardium. Diagnostic tools include ECG, CT, and MRI, with MRI being the most effective option. Currently, there is no consensus on the best treatment plan; however, immunotherapy is the most employed treatment option. Immune checkpoint inhibitors, such as PD-1 and CTLA-4 inhibitors, have improved response and survival rates in patients with advanced melanoma. These treatments are considered the standard of care. In fact, due to their effectiveness, chemotherapy is no longer recommended to treat metastatic melanoma. Non-curative surgeries, such as conservative excisions of cardiac tumours, are performed solely to alleviate symptoms and enhance quality of life. Despite the global rise in melanoma incidence and meaningful prognostic advances achieved with modern immunotherapy, outcomes for patients with cardiac metastases remain poor. The significant prevalence of cardiac involvement in advanced melanoma, coupled with its association with low survival rates and frequent late detection, represents a clinically significant yet underrecognized problem that warrants greater research focus and dedicated investigation.

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NARRATIVE REVIEW
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The roles of perivascular adipose tissue in obesity-related hypertension

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ABSTRACT

Background: Obesity and hypertension (HTN) are two of the most prevalent and pressing current global health issues due to their associated morbidity and mortality. Obese individuals are more susceptible to developing HTN. Perivascular adipose tissue (PVAT) has been posited to be the fourth layer of the normal arterial wall. PVAT can modulate vascular tone, vascular endothelial function, and vascular smooth muscle cell growth and proliferation, contributing to HTN.

Results: In obesity-related HTN, PVAT exhibits abnormal vasoactive adipokine production and immune cell recruitment as well as enhanced inflammation, which exacerbate blood pressure elevation and lead to target organ damage. Distinct immune cell populations have been identified to infiltrate PVAT, which can become potential therapeutic targets.

Conclusion: This paper reviews PVAT dysfunction in obesity-related HTN, highlighting the vasoactive factor release, immune cell infiltration, and inflammation, as well as implications for therapeutic approaches.

KEYWORDS
Obesity, Hypertension, Perivascular adipose tissue, Inflammation, Immune cells

1 | INTRODUCTION

1.1 | Overview of obesity

Obesity is a chronic and multisystem condition which is associated with increased morbidity and mortality worldwide. Excessive fat deposits generate unfavourable hemodynamic modifications, dysregulate fatty acid and glucose metabolism, trigger insulin resistance and inflammation, and eventually damage several organs. (1) According to the World Health Organization (WHO), the global prevalence of adult obesity has more than doubled since 1990, and that of adolescent obesity has quadrupled. (2) In 2022, 43% of adults aged 18 and older (2.5 billion adults) were overweight, and 16% (890 million adults) were obese. Over 390 million children and adolescents aged five to 19 were overweight, including 160 million who were obese. Alarmingly, 37 million children aged

five and younger were overweight. If there are no breakthroughs in obesity management, the worldwide cost of overweight and obesity can reach three trillion US dollars per year by 2030.

Obesity is diagnosed by calculating the body mass index (BMI) that is weight (kilograms) divided by height squared (metres squared). Table 1 specifies the classification of whether a White, Hispanic, or Black individual is underweight, normal weight, overweight, or obese based on BMI as used by the National Institute of Health (NIH) and WHO. (3) As the cut-offs underestimate the obesity risks in the Asian and South Asian populations, an Asian and South Asian individual may be deemed overweight and obese with a lower BMI (BMI of 23-24.9 kg/m2 to be overweight and BMI of more than 25 kg/m2 to be obese). In 2019, higher-than-optimal BMI was estimated to result in five million deaths from noncommunicable diseases, comprising cardiovascular diseases (CVDs). (4) However, because individual variations exist, and BMI does not differentiate between lean muscle mass and adipose tissue mass, BMI is insufficient as the sole means of determining whether an individual is obese. (1, 3) Furthermore, an obesity paradox has been noted, whereby obesity evaluated by BMI may be benign rather than have pathological consequences. (1) Girth, which is abdominal circumference as evaluated by the waist/hip ratio, may be a better way to assess pathological obesity. This phenomenon manifests as a contrast between apples (increased abdominal circumference) and pears (increased hip circumference) – the former associated with cardiometabolic pathological conditions including CVDs, diabetes, and metabolic dysfunction-associated fatty liver disease (MAFLD), all leading to higher mortality.

1.2 | Overview of hypertension

High blood pressure (BP), systemic hypertension (HTN), or HTN is the leading risk factor for global disease burden and mortality. HTN causes chronic inflammation and predisposes to multiple detrimental complications in the cardiovascular system, kidneys, brain, and mental health, including cognitive decline and dementia. (5) According to WHO's report on HTN in 2023, the number of individuals with HTN doubled from 650 million to 1.3 billion between 1990 and 2019. Among individuals aged 30 to 79 with HTN, only 54% have been diagnosed, 42% are being treated, and 21% are considered to have the condition controlled. If countries can mobilize to achieve WHO's goal of 50% population HTN control by the year 2050, 76 million cardiovascular deaths and 450 million disability-adjusted life years may be avoided. In addition, the economic benefits may be 18 times greater than business as usual.

HTN has been defined by the BP levels at or above which reducing BP will decrease the cardiovascular risks associated with elevated BP. (6) This threshold has classically been 140/90 mm Hg based on actuarial data from the insurance industry. Nevertheless, it is worth noting that among individuals aged 40 to 69, cardiovascular risks progressively rise from as low as 115/75 mm Hg with a two-fold escalation in death rates from cardiovascular causes for every 20/10 mm Hg increment. (7) Furthermore, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that hypertensive individuals at high risk of CVDs with systolic BP (SBP) of 130-180 mm Hg would benefit from reducing SBP to below 120 mm Hg. (8) Thus, the new threshold has been proposed to be 130/80 mm Hg for hypertensive individuals at high cardiovascular risk: chronic kidney disease patients, diabetic people, elderly people, and people with a Framingham Risk Score of 15% or higher. (6) In fact, the 2017 American Heart Association/American College of Cardiology guideline for HTN management has defined HTN for all individuals as BP at or above 130/80 mm Hg. (9) Although there is not a different BP cut-off for obese individuals, these people are 3.5 times more susceptible to developing HTN.(10) In fact, the Framingham Heart Study revealed 60-70% of HTN is caused by obesity.

1.3 | Adipose tissue, particularly perivascular adipose tissue, plays a role in obesity-related hypertension

Massive expansion and remodelling of adipose tissue in obesity exert differential impacts on specific adi-

Classification		BMI number
Severely underweight		Less than 16.5 kg/m^2
Underweight		Between 16.6 kg/m^2 and 18.5 kg/m^2
Normal weight		Between 18.6 kg/m^2 and 24.9 kg/m^2
Overweight		Between 25 kg/m^2 and 29.9 kg/m^2
Obesity	Obesity class I	Between 30 kg/m^2 and 34.9 kg/m^2
	Obesity class II	Between 35 kg/m^2 and 39.9 kg/m^2
	Obesity class III (also known as severe, extreme, or massive obesity)	More than 40 kg/m^2

TABLE 1 Classification of whether a White, Hispanic, or Black individual is underweight, normal weight, overweight, or obese based on BMI as used by the National Institute of Health (NIH) and World Health Organization (WHO). (3)

pose tissue depots that have differential contributions to chronic systemic inflammation and HTN. (11) Initially thought to be exclusively an energy-storing organ, adipose tissue has been recognized to be highly dynamic and responsible for several processes, including metabolism and modulation of vascular tone. Adipose tissue can be categorized based on the cellular composition as white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue. During pregnancy, lactation, and post-lactation, subcutaneous WAT can transdifferentiate into pink adipose tissue. Adipose tissue can also be categorized based on the anatomical localization as visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), gluteofemoral adipose tissue (GAT), epicardial adipose tissue (EAT), and perivascular adipose tissue (PVAT). The focus of this paper – PVAT – is a heterogenous, metabolically active, endocrine organ surrounding most blood vessels, except cerebral and pulmonary ones. (12) Obesity is associated with an increase in PVAT mass and PVAT dysfunction, contributing to obesity-related HTN and target organ damage.

2 | DISCUSSION

2.1 | Obesity induces PVAT dysfunction

Obesity-induced PVAT dysfunction results from lipid spillover, hypoxia, and adipocyte apoptosis. Typically, the healthy PVAT consists of white-like and brown-like adipocytes, immune cells, stem cells, microvasculature, and nerves, but the exact phenotype depends on the anatomical location and may vary with the individual's health status.(12) Obesity is characterized by excess fatty acids stored in adipocytes that may be increased in number but mostly in size. (13, 14) Despite exhibiting some WAT histological properties, perivascular adipocytes are less differentiated and have less lipid storage capacity than white adipocytes. (15) Therefore, lipid spillover, ectopic fat deposition, and lipotoxicity occur after the storage capacity of perivascular adipocytes is exceeded. (13) Because the hypertrophic expansion of perivascular adipocytes is not supported by a similar rise in angiogenesis rates, some adipocytes are left outside of the existing vasculature's oxygen diffusion zone, resulting in hypoxia and vasoconstriction.(16) Oxidative stress is enhanced as nitric oxide

synthase uncoupling results in the production of superoxide instead of nitric oxide (NO). (14) Due to the increased reaction between superoxide and NO, vascular nitrotyrosine (a marker of peroxynitrite production) increases with nitration of proteins and leads to their dysfunction. Moreover, the aldosterone levels elevate in obesity, upregulating the expression of VCAM-1 (vascular adhesion molecule-1), PECAM-1 (platelet endothelial cell adhesion molecule-1), and ICAM-1 (intercellular adhesion molecule-1) as well as activating the NLRP3 (NLR family pyrin domain containing 3) inflammasome. (14, 17, 18) Consequently, dysfunctional perivascular adipocytes display abnormal Toll-like receptor signalling, vasoactive adipokine secretion, and immune cell recruitment. (13, 19) Adipocyte apoptosis happens when perivascular adipocytes can no longer tolerate the stress signals of nutrient overload and oxidative stress. (13) Despite evidence that brown-like adipocytes in PVAT may counterbalance the white-like ones and counteract obesity-induced cardiometabolic disorders, there is also evidence that BAT activation increases heart rate and becomes detrimental to cardiovascular health. (20, 21) Overall, obesity severely disrupts PVAT's homeostasis via various mechanisms involving NO production, vasoactive adipokine release, immune cell infiltration, and inflammation, thereby contributing to obesity-related HTN.

2.2 | PVAT produces vasoactive factors implicated in obesity-related hypertension

PVAT has been argued to be the fourth layer of the normal arterial wall (tunica adiposa) since the tissue is capable of modulating vascular tone, vascular endothelial function, and vascular smooth muscle cell (VSMC) growth and proliferation, leading to HTN. (12, 14) PVAT triggers both vasodilatation and vasoconstriction via endocrine and paracrine mechanisms. Multiple studies have shown that PVAT loses its anticontractile effects and potentiates vasoconstriction under certain pathophysiological conditions comprising obesity and HTN. (14, 22)

2.2.1 | Anticontractile PVAT-derived factors

PVAT-derived adiponectin, hydrogen sulphide (H2S), angiotensin (Ang) 1-7, and NO have been the focus of many studies as vasodilators that protect against obesity-related HTN in animal models and humans. Adiponectin in different polymeric forms causes vasodilatation by acting on vascular endothelial cells and VSMCs, in addition to downregulating plasma glucose levels and impacting macrophage polarization. (23) H2S also triggers vasodilatation via endothelium-dependent and -independent mechanisms besides mediating oxidative stress, macrophage polarization, and inflammation. (24) Ang 1-7, a member of the renin-angiotensin-aldosterone system (RAAS), induces vasodilatation via endothelium-dependent mechanisms and restores glucose tolerance. (25, 26) These anticontractile PVAT-derived factors stimulate NO production, which can directly elicit vasodilatation following diffusion to VSMCs or indirectly by increasing adiponectin. (22, 27) Based on animal models, other anticontractile PVAT-derived factors may include palmitic acid methyl ester and omentin; however, more research is needed. (28, 29) Regardless, all mentioned factors have been detected to decline in obesity and HTN.

2.2.2 | Pro-contractile PVAT-derived factors

PVAT-derived superoxide anion, aldosterone, Ang II, and prostaglandins counteract anticontractile PVAT-derived factors and cause vasoconstriction, resulting in obesity-related HTN. Superoxide anion is a free radical oxygen species, which enhances vasoconstriction in obese animal models by raising oxidative stress as well as lowering H2S and NO bioavailability. (14) Superoxide anion production can be stimulated by aldosterone and Ang II, final mediators of the RAAS and in the case of Ang II, an antagonist of Ang 1-7. (18, 26, 30) Aldosterone and Ang II elicit oxidative stress generation, vasoconstriction, and immune cell recruitment in obese animal models and humans. These pro-contractile PVAT-derived factors have been documented to increase in obesity and HTN. On the other hand, prostaglandins – arachidonic acid-derived metabolites – assume different roles de-

pending on the individual's health status. For instance, prostaglandins augment serotonin- and phenylephrine-induced vasoconstriction of the aorta from obese mice but not lean ones. (31) The roles of chemerin and resistin in vasoconstriction and obesity-related HTN have also been suggested in animal models. Chemerin positively correlates with insulin resistance, more sympathetic nerve-induced vasoconstriction, and immune cell infiltration.(32, 33) Primarily secreted by macrophages, resistin attenuates insulin-related and endothelium-dependent, bradykinin-induced vasodilatation as well as promotes pro-contractile endothelin-1 (ET-1) expression. (34, 35)

2.2.3 | PVAT-derived factors exhibiting both anticontractile and pro-contractile properties

PVAT-derived leptin, hydrogen peroxide (H2O2), and catecholamines demonstrate anticontractile and pro-contractile properties via different mechanisms, depending on the individual's health status and the factor's concentration. In addition to controlling appetite, energy expenditure, and body weight, leptin causes vasodilatation by targeting vascular endothelial cells and VSMCs in animal models. (36) However, obesity-induced chronically high leptin levels trigger more ET-1 release, contributing to vasoconstriction and higher peripheral resistance. (36, 37) Similarly, H2O2 elicits vasodilatation by influencing vascular endothelial cells and VSMCs, but obesity-induced higher H2O2 levels lead to vasoconstriction in animal models and humans.(19) Human perivascular adipocytes can synthesize catecholamines de novo or take up and store catecholamines from the sympathetic nervous system, forming a reservoir of noradrenaline, dopamine, and serotonin that causes vasoconstriction. (38) In contrast, immune cells in PVAT of animal models can secrete catecholamines that enhance adiponectin and NO production, triggering vasodilatation. (39, 40) Recently, visfatin has been investigated for its potential roles in vasoconstriction, endothelial dysfunction, and stimulated VSMC proliferation in small resistance arteries of rats and humans but vasodilatation in large conduit arteries of rats.(41, 42) Higher visfatin levels are observed in hypertensive obese individuals. (43)

2.3 | Immune cells in PVAT contribute to obesity-related hypertension

In response to obesity-induced inflammation, innate and adaptive immune cells in PVAT undergo several changes. As first confirmed in 2010 by Viel and co-authors, inflammation and the immune system play an essential role in HTN.(17) Immune cells interact with one another, crosstalk with perivascular adipocytes, and modify the vascular reactivity in obesity-related HTN.

2.3.1 | Innate immune cells

Neutrophils, mast cells, and dendritic cells (DCs) contribute to obesity-related HTN. Neutrophils are early responders to obesity: transiently rise in obese individuals and secrete elastase that enhances glucose intolerance and insulin resistance. (44, 45) Furthermore, obesity-induced higher levels of circulating neutrophils and accumulated neutrophils in microvasculature positively correlate with BP in animal models and humans. (44, 46, 47) Neutrophils regulate vascular dysfunction by generating superoxide anion, augmenting oxidative stress, and reducing NO bioavailability. Additionally, neutrophil extracellular traps (NETs) are created by neutrophil-derived extracellular DNA strings in mice upon Ang II stimulation. (44, 45) NETs promote endothelial damage and exert prothrombotic properties. As one of the first cell populations to migrate to inflammation sites, neutrophils facilitate the recruitment of DCs, macrophages, and lymphocytes. DCs significantly increase from negligible levels in the lean phenotype to levels comparable to macrophages in mice following a high-fat diet. (48, 49) The larger DC population in PVAT has been linked to oxidative stress, impaired anticontractile properties, and overproduction of proinflammatory cytokines. (50, 51) As antigen-presenting cells, DCs also play a critical role in activating T cells. Upon Ang II stimulation, DCs produce IL-23 that regulates the differentiation and maintenance of IL-17-producing T cells. Moreover, a subclass of DCs – plasmacytoid DC – causes vasoconstriction and HTN in response to PVAT-derived chemerin. (32) Nevertheless, because DCs and macrophages all express CD11b and F4/80, it has been complicated to iso-

late the roles of PVAT-derived DCs and macrophages in obesity and HTN. (48) The number of mast cells also increases in obese animal models and humans, and control of the mast cell population using pharmacological stabilizers can mitigate obesity in mice. (52) However, the specific roles of mast cells in obesity remain controversial. Some researchers believe that mast cells directly take part in insulin resistance and the onset of obesity, whereas others claim that mast cells play no essential roles in obesity. (52, 53) Regardless, mast cells are implicated in PVAT's mediation of the vascular tone by triggering local acute inflammatory responses in animal models.(45)

In 2005, De Ciuceis and co-authors were the first to identify the roles of a specific individual immune cell population – macrophages – in the development of experimental HTN. (54) Macrophages exhibit higher numbers and activation levels in obese and hypertensive patients via autocrine signals and interactions with other immune cell populations. (12) As previously mentioned, macrophages are the primary source of resistin that positively correlates with BP in humans. (35) Macrophage polarization assumes a crucial role in the proinflammatory shift in response to obesity.(55) Specifically, aldosterone, chemerin- and neutrophil-stimulated increase of M1 macrophages is associated with insulin resistance, atherosclerosis, and HTN as M1 macrophages induce oxidative stress, decrease H2S bioavailability, and release proinflammatory cytokines. (18, 24, 32, 44, 56) Meanwhile, adiponectin-, H2S-, and eosinophil-stimulated increase of M2 macrophages counteracts M1 macrophages and maintains PVAT's homeostasis via adipocyte turnover, lipid buffering, and modulation of sympathetic drive. (55, 57) Nevertheless, because macrophages are late responders to obesity, the significance of their interactions with other immune cell populations remains a matter of debate.

In contrast to other innate immune cell types, the number of eosinophils in mice declines in response to a high-fat diet. (58) Eosinophil-deficient mice have been proven to display impaired glucose tolerance, lose PVAT's anticontractile properties, and have high peripheral resistance, which may be rescued by eosinophil reconstitution. (40, 45) Eosinophils maintain PVAT's homeostasis and elicit vasodilatation by producing interleukin (IL)-4 and IL-13 and sustaining M2 macrophage polarization. (39, 40, 57)

2.3.2 | Adaptive immune cells

Shortly following a high-fat diet, the total B-cell number as well as the cell numbers of the B-1 and B-2 subpopulations in mice all rise and correlate with Ang II-induced BP elevation. (59, 60) B cell-deficient obese mice are protected against obesity-related diseases in spite of weight gain. (61) Specifically, B-2 cells aggravate insulin resistance and atherosclerosis in mice by secreting atherogenic IgG antibodies and promoting proinflammatory T cells, whereas B-1 cells assume the opposing, protective role and attenuate glucose intolerance, vascular dysfunction, and inflammation in mice and humans by releasing atheroprotective IgM antibodies. (60, 61) How the two B-cell subpopulations act on vascular function is particularly interesting, considering that the B-1/B-2 ratio is ten-fold higher in murine PVAT than in the spleen and bone marrow.

The conventional alpha/beta ($\alpha\beta$) T-cell subpopulations undergo different changes in obesity: the frequencies of proinflammatory $CD8^+$ cytotoxic T (T_c2) cells, $CD4^+$ helper T-1 (T_h1) cells, and $CD4^+$ helper T-17 (T_h17) cells rise, while those of anti-inflammatory $CD4^+$ helper T-2 (T_h2) cells and $CD4^+$ or $CD8^+$ regulatory T (T_{reg}) cells decline. (17, 30) T_c cells play an important role in both the initiation and maintenance of obesity, inflammation, and HTN in animal models and humans. (62, 63) CD8-deficient animal models have less glucose intolerance, proinflammatory cytokine production, and hypertensive responses to Ang II. Furthermore, it is well-known that T_h1 and T_h2 cells counteract and inhibit the cytokine secretion of the other. (45, 64) T_h1 cells release proinflammatory IL-2, interferon (IFN)-γ, and tumour necrosis factor (TNF)-α and support M1 macrophage polarization, whereas T_h2 cells produce anti-inflammatory IL-4 and enhance M2 macrophage polarization. (63, 64) Since the T_h1/T_h2 ratio increases in obese animal models and humans, proinflammatory cytokine secretion and M1 macrophage polarization by T_h1 are favoured, resulting in more vascular dysfunction and inflamma-

tion. (64) Meanwhile, more IL-17 is released by T_h17 cells in obese animal models and humans, contributing to and sustaining HTN as the proinflammatory cytokine augments oxidative stress and impairs vascular function. (45, 63) IL-17 can also be produced by the unconventional innate-like gamma/delta ($\gamma\delta$) T-cell population that is increased in obesity and promotes insulin resistance and inflammation. (45, 50, 51, 63, 65) Mice devoid of $\gamma\delta$ T cells are protected against Ang II-induced BP elevation, vascular dysfunction, and T-cell activation in PVAT. (66) CD28 is a co-stimulatory T-cell receptor that plays a role in $\gamma\delta$ T-cell survival and proliferation. (67) CD28-expressing δ T cells are elevated in PVAT of hypertensive mice and SAT of obese humans. The total T_{reg}-cell number is reduced in obese animal models and humans, along with their beneficial mediation of insulin resistance, vascular dysfunction, and immune homeostasis via cell-cell contact mechanisms and anti-inflammatory cytokine release. (17, 50, 63) In 2011 and 2012, the Schiffrin research group published two papers proving the protective roles of $CD4^+$ T_{reg} cells against both aldosterone- and Ang II-induced vascular injury and HTN in mice.(56, 68) Although not examined in PVAT, $CD8^+$ T_{reg} cells have recently been detected with higher percentages within the $CD8^+$ T-cell population in the circulation, VAT, and SAT of obese humans, possibly as a compensatory mechanism for the smaller $CD4^+$ T_{reg}-cell population. (69)

2.4 | Therapeutic approaches to obesity-related hypertension

The non-pharmacological interventions to relieve obesity-related HTN are lifestyle modifications and bariatric surgery. The first recommended management strategy, lifestyle modifications, has been emphasized by different guidelines as a non-invasive, inexpensive, and sustainable method to alleviate obesity-related HTN. (9) In fact, lifestyle modifications are essential to support and maintain the effects of bariatric surgery and pharmacological interventions. Regular physical activity helps decrease perivascular adipocyte size and proinflammatory markers (e.g., leptin, TNF-α) and immune cells (e.g., M1 macrophages) as well as enhancing anti-inflammatory markers (e.g., adiponectin, NO) and immune cells (e.g., M2 macrophages). (19) Similarly, dietary interventions (e.g., DASH diet, Mediterranean diet, intermittent fasting diet) can improve the metabolic profiles and lower inflammation.(70) Therefore, PVAT inflammation is reversed, PVAT function restored, and blood glucose levels and BP normalized.(19, 70) However, lifestyle modifications can be insufficient as a stand-alone therapy because individuals may be unable to adhere to the exercise and diet regimen, requiring pharmacological and surgical interventions in addition. (71) Bariatric surgery is an invasive approach with some associated risks, especially for individuals in obesity classes II and III. (72) The success of the surgery necessitates the appropriate procedures, as well as a holistic and individualized treatment plan to consider the patient's nutritional and psychosocial attributes before, during, and after the surgery to avoid long-term complications (e.g., excessive weight loss, nutritional deficiencies, and gastrointestinal and renal problems). Successful bariatric surgery can reduce proinflammatory markers and immune cells as well as promote anti-inflammatory markers and immune cells, restoring PVAT function, normalizing BP, and improving metabolic control after six months. (73)

The main pharmacological interventions to ameliorate obesity-related HTN are the RAAS inhibitors, immunomodulatory drugs, and the more recently introduced glucagon-like peptide-1 (GLP-1) agonists (e.g., daily liraglutide or weekly semaglutide), double GLP-1 agonists, and glucagon inhibitory peptide (GIP) agents (e.g., weekly tirzepatide). (18, 30, 51, 71, 74) Firstly, it is worth noting that the effectiveness of anti-obesity medications in decreasing BP varies based on the drug's mechanism of action and the individual's characteristics.(71, 74) Weight-loss medications lead to insufficient BP lowering in most cases and should not be used for individuals with HTN in some cases. Consequently, anti-hypertensive medications are ultimately prescribed for obesity-related HTN. Anti-hypertensive medications include diuretics (especially long-acting ones), RAAS inhibitors, calcium channel blockers, all first-line agents, mineralocorticoid receptor antagonists, and adrenergic blockers. Anti-hypertensive medica-

tions targeting the RAAS (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and renin inhibitors, although the latter mostly abandoned) demonstrate a broad spectrum of benefits on HTN and the cardiovascular system. Additionally, ACE inhibitors and ARBs exert favourable influences on lipid and glucose abnormalities in obesity. Immunomodulatory drugs have recently received much attention thanks to advances in the understanding that immune mechanisms may be driving obesity and HTN. (18, 30, 51) Protection against obesity, HTN, and comorbidities by inhibition of cytokines and immune cells in experimental animal models suggests potential therapeutic approaches. Moreover, advances in technology (e.g., nanoparticles to deliver immunosuppressants) can support drug innovation and novel treatment strategies. (75) However, comprehensive knowledge of the immune mechanisms in obesity and HTN must be acquired before the available evidence from experimental animal models can be translated into various clinical HTN phenotypes.

3 | CONCLUSION

The complex interplay between obesity and HTN underscores the necessity for a multifaceted approach to prevention and treatment. Obesity predisposes an individual to HTN via several mechanisms, particularly involving the roles of PVAT. As a heterogenous, metabolically active, endocrine organ surrounding most blood vessels, PVAT regulates vascular tone, vascular endothelial function, and VSMC growth and proliferation. In obesity-related HTN, PVAT becomes dysfunctional. The tissue exhibits abnormal vasoactive adipokine secretion and immune cell infiltration as well as augmented inflammation. Because lifestyle modifications can reduce obesity-related HTN but may be insufficient as a stand-alone treatment, pharmacological and surgical interventions may be required. Given the goals of simultaneously alleviating two conditions and that individual variations exist, therapeutic approaches should be made in a personalized way. Recently, immunomodulatory drugs have emerged as a promising therapeutic approach. However, further research on the immune mechanisms in obesity and HTN must be achieved to formulate effective drugs and mitigate the pressing worldwide health and economic impact of obesity-related HTN.

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Case Report



CASE REPORT
McGill Journal of Medicine

Hypomagnesemia and hypocalcemia due to long standing proton pump inhibitor use: A severe side effect of a commonly prescribed drug

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ABSTRACT

Proton pump inhibitors (PPIs) are amongst the most prescribed medications in Canada. However, they are not without risk. While there are many acute and chronic reasons for the use of these drugs, they are often prescribed with no clear indication. In this case, we describe a patient who chronically used a PPI and presented with severe hypomagnesemia and profound hypocalcemia, which caused a collapsed esophagus. After extensive workup, it was deemed that his electrolyte imbalances were most likely due to his chronic PPI use, and his symptoms quickly improved with electrolyte replacement and cessation of the drug. This case illustrates the importance of judicious use of even the most used medications and argues for monitoring of electrolytes for those who use PPIs chronically.

LEARNING POINTS

- Review the many side effects associated with a commonly prescribed medication class: proton pump inhibitors, and review indications for their use.
- Reinforce the importance of deprescribing unnecessary medications.
- Emphasize the importance of keeping adverse drug reactions in the differential when assessing electrolyte abnormalities.

KEYWORDS
Adverse drug reaction, Deprescribing habits, Electrolyte Imbalances

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used medications, being the second most prescribed drug class in Canada behind statins, with 2.7 million users being prescribed these medications in 2021 alone (1). PPIs have several acute and chronic indications. Acute indications include duodenal and gastric ulcer treatment, part of the triple therapy regimen for Helicobacter pylori infections, and stress ulcer prophylaxis in critically ill patients. Indications for long-term usage include previous GI bleed, severe (Grade D) esophagitis, prevention of nonsteroidal anti-inflammatory drug-induced ulcers, and hypersecretory conditions such as Zollinger-Ellison

syndrome (2, 3, 4). Evidence shows that PPIs are, for the most part, safe in the short-term, with the serious adverse events tending to be associated with chronic use. In a large claims-based analysis of over 1.7 million adults, approximately 28% of newly prescribed proton pump inhibitor (PPI) courses were classified as potentially inappropriate based on cumulative dose and duration exceeding guideline recommendations (5). The incidence of potentially inappropriate PPI prescribing increased over time, rising from 4.8% to 6.4% of the general population between 2013 and 2017 (5). This all together results in a significant population using PPIs chronically. Documented adverse effects of long-term PPI therapy include increased susceptibility to enteric infections (such as Clostridioides difficile), community-acquired pneumonia, micronutrient deficiencies such as hypomagnesemia and vitamin B12 deficiency, and impaired calcium absorption with an associated risk of osteoporotic fractures. These drugs have also been linked to acute interstitial nephritis that could lead to the development of chronic kidney disease. Additional reported associations include small intestinal bacterial overgrowth and possible cardiovascular, cognitive, and renal effects, though the strength of evidence varies across these conditions (4, 6). Furthermore, PPIs further complicate polypharmacy by having a myriad of drug interactions and affecting the absorption of other medications due to their effects on the gastric pH (7). These adverse events can easily be missed among chronic users in the community, and this can have dangerous consequences, as illustrated in the case below.

2 | CASE DESCRIPTION

The patient was a 75-year-old male known for chronic obstructive pulmonary disease (COPD), hypertension, a history of previous cerebrovascular accident, C7 radiculopathy, and severe GERD. He presented to the hospital with shortness of breath and stridor in the context of severe worsening dysphagia to liquids in the past three weeks. The patient decided to come to the emergency department as he felt his “throat was closing up”. He indicated that he also had experienced involuntary hand spasms the day before presentation and had paresthesia in his hands and feet in the past couple of weeks. He denied any nausea, vomiting, diarrhea, constipation, weight loss, fevers, or night sweats. He was previously well until his symptoms started.

His medications at home included Aspirin 80 mg daily, Bisoprolol 5 mg daily, Atorvastatin 40 mg daily, Amlodipine 5 mg daily, Valsartan 160 mg daily, Magnesium Gluconate 500 mg daily, and Calcium Carbonate 500 mg daily, as well as Pantoprazole 40 mg daily. He endorsed taking Pantoprazole daily for the past five years. His hypomagnesemia had been noted as a previous concern, and as such, he was already prescribed magnesium supplementation by his primary care provider.

Physical examination revealed a man with slightly increased work of breathing but otherwise well. His blood pressure was 138/78 mmHg, his heart rate was 65 bpm and his oxygen saturation was 95% on room air. There was no tetany found on neurological examination and he had a negative Chvostek’s sign but had a positive Trousseau’s sign. His electrocardiogram at presentation showed a prolonged corrected QT interval of 474 ms.

Initial laboratory tests showed that he had severe hypomagnesemia at 0.21 mmol/L (normal: 0.70-1.23 mmol/L) and severe corrected hypocalcemia at 1.21 mmol/L (normal: 2.12-2.62 mmol/L). A CT scan of his head and neck demonstrated a collapsed esophagus but no other major abnormalities. Given his severe electrolyte disturbances, he was given 5 g of intravenous (IV) magnesium as well as 1 g of IV calcium gluconate.

At this point, the etiology of his electrolyte abnormalities was unclear and the differential for these abnormalities was quite broad. Hypomagnesemia is normally caused by one of three reasons: decreased intake, increased excretion, or sequestration. Decreased intake is often in the context of malnourishment, cachexia, or severe alcoholism. Sequestration is caused by shifts of magnesium from extracellular to intracellular compartments, often in the context of an acute correction from a metabolic insult, such as diabetic ketoacidosis treatment, correction of acidosis, or refeeding syndrome. Fi-

Laboratory Investigations	Result	Reference Range
Serum parathyroid hormone	127 ng/L	10-70 ng/L
Serum vitamin D-O25	86 nmol/L	75-250 nmol/L
Serum 1-25 Vitamin D	60 pmol/L	90-174 pmol/L
Urine magnesium	2.8 mmol/day	3.0-5.0 mmol/day
Urine potassium	22 mmol/day	25-125 mmol/day
Urine calcium	3.01 mmol/day*	2.5-7.5 mmol/day
Urine creatinine	8.8 mmol/day	7.1-15.9 mmol/day

* Urinary calcium was not as low as expected due to urine tests being done after calcium replacement.

TABLE 1 Results of investigations to assess the cause of hypocalcemia and hypomagnesemia

nally, increased excretion is either through the GI tract (laxative abuse, diarrheal illnesses, malabsorption syndromes) or the kidney (diuretic use, renal injury/failure, or congenital disorders such as Gittleman's) (8).

On the other hand, hypocalcemia can be caused by several reasons. When approaching hypocalcemia, one can divide causes into PTH dependent, PTH independent, and other causes. PTH dependent causes involve hypoparathyroidism and the disruption of the body's ability to regulate calcium homeostasis. This is often due to the destruction or removal of the parathyroid gland. PTH independent causes of hypocalcemia are varied and include certain drugs (Foscarnet and bisphosphonates), Vitamin D deficiency, metabolic abnormalities (severe acidosis and alkalosis) and severe illness states such as sepsis and pancreatitis. Moreover, hypomagnesemia itself can be a cause of hypocalcemia, as low magnesium can cause induced PTH resistance (9).

Further investigation was done to elucidate the etiology of hypomagnesemia and hypocalcemia (Table 1). The serum investigations yielded appropriately high PTH, sufficient levels of vitamin D-25 OH and low levels of 1-25 Vitamin D. This indicated secondary hypoparathyroidism, likely secondary to hypomagnesemia. The urine electrolytes showed low levels of magnesium, low levels of potassium, and normal levels of calcium. This was indicative of no renal wasting of electrolytes, which made a renal pathology less likely. Thus, upon consultation with Nephrology and Endocrinology, it was determined that the etiology was likely chronic proton pump inhibitor use, causing poor absorption and increased excretion of magnesium through the patient's GI tract.

The patient was admitted to an Internal Medicine ward and given IV replacement of magnesium and calcium. The proton pump inhibitor (pantoprazole) was discontinued, and the patient was prescribed H2 antagonists for his gastric reflux symptoms. Within two days, the patient's magnesium and calcium levels normalized. His symptoms resolved, and he was discharged home with close follow up with Endocrinology as well as an outpatient Gastroenterology consultation for investigation of his refractory gastroesophageal reflux.

The patient was seen in the clinic one week after discharge with follow up blood work, and his magnesium and calcium levels were stable and within normal limits. However, he continued to have severe GERD, which will be assessed by his Gastroenterologist.

3 | DISCUSSION

Despite being generally well tolerated medications, PPIs are not without risk. There are both known and unknown side effects of PPI use. Complications from chronic PPI use, such as acute interstitial nephritis, malabsorption of micronutrients and vitamins, and gastric

hyperplasia, are well documented (6, 7). However, there are widespread theoretical risks associated with gastric hypoacidity and disruption of the intestinal microbiota. Observational studies have found an association between PPI use and an increased risk for Clostridium Difficile infection, liver disease, and dementia (6). The pathophysiology of these side effects is not well understood. It is thought that the decrease in the acidity of the gastric pH can cause malabsorption of nutrients since many depend on being bound by proteins to be absorbed, and changes in acidity can cause proteins to misfold and decrease absorption (6). Moreover, mechanistically, an increase in gastric pH has been proposed to decrease gastric protection to harmful bacteria and change gut microbiota composition (6). The effects of microbiome-human host interaction is an evolving field, but the modification in this interaction is thought to be the culprit of many of the side effects seen in PPIs (6). Thus, it can be confidently said that we do not yet know the side effects and possible implications of chronic PPI use.

The dangers of inappropriate PPI use are a well-recognized issue, and current recommendations exist to reduce unnecessary use of these medications. For example, PPIs are a part of the American Geriatrics Society Beer's Criteria® for potentially inappropriate medications (10). In addition, efforts are being made to encourage physicians to deprescribe these medications (2, 3). However, the uptake for this has been slow, and these medications are still quite commonly prescribed in an inappropriate manner. Therefore, it is important for physicians to always consider deprescribing and to have frank discussions with their patients about the risks and benefits of these medications. As such, every patient encounter is an opportunity to deprescribe.

Despite the proven side effects of PPIs, current guidelines do not recommend routine laboratory monitoring for patients on chronic proton pump inhibitor therapy. In fact, the expert opinion is that the best way to avoid long term complications of PPIs is to avoid prescribing them inappropriately and prescribing the minimum effective dose when they are indicated (11). As a result, for the clinician who encounters patients in the inpatient setting with unexplained electrolyte abnormalities, it is important to keep the adverse effects of proton pump inhibitors in their differential.

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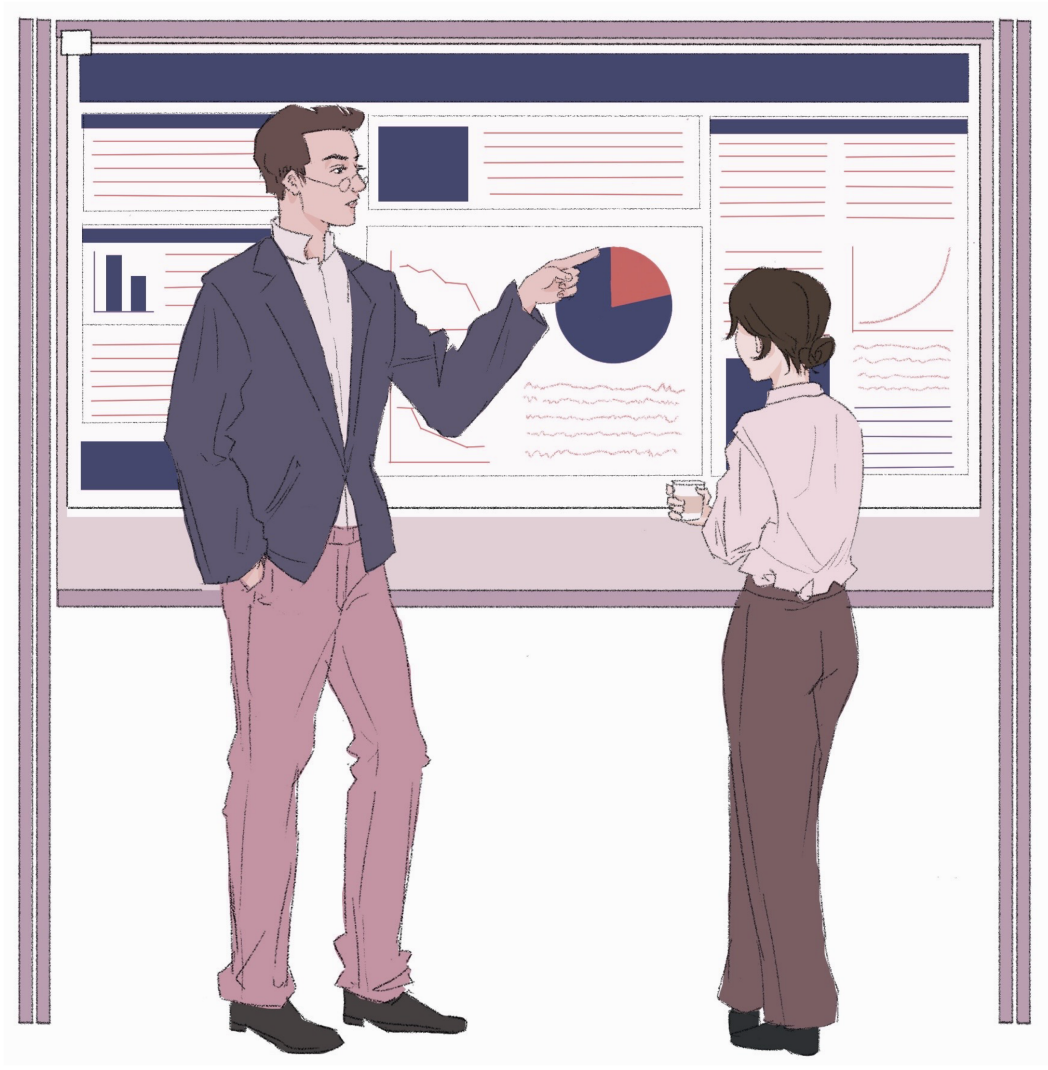
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Commentary



COMMENTARY
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Using Gamification to Improve Medical Student Education: An Emphasis on Anatomy, Pathology, and Pharmacology

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ABSTRACT

Traditionally, medical training utilized rote memorization strategies, didactic lectures, and dissections of cadaveric donors to convey information. As significant as these traditional methodologies have been in shaping medical training, they often fail to maintain student engagement and do not always foster the deep conceptual understanding necessary for clinical proficiency. Given the high cognitive loads experienced by medical students, new methodologies that maximize motivation, recall, and hands-on practice are increasingly researched. Gamification, defined as the integration of game elements such as points, levels, rewards, leaderboards, and interactive simulations, has gained traction as an effective educational tool.

This article addresses the use of gamification in medical education, namely in pathology, anatomy, and pharmacology. Empirical studies are utilized to examine how educational tools with a gamified format enhance motivation, problem-solving, and the application of information. Key advantages include increased student engagement, improved recall, and a more interactive approach to medical training. However, challenges such as cognitive overload, varied student preferences, and resource constraints are also analyzed. By evaluating the effectiveness and limitations of gamification, this paper contributes to a growing discourse on innovative educational strategies that can improve medical training, with the goal of better preparing students for clinical practice.

KEYWORDS
Gamification, Medical Education, Anatomy, Pathology, Pharmacology

1 | INTRODUCTION

Traditionally, medical training involved didactic lectures, dissection of cadaveric donors, and immense levels of memorization to impart information. As beneficial as these approaches have proven in shaping medical training, in many instances, they have struggled to maintain students' motivation. (1) Additionally, modern learning environments introduce new challenges to sustained attention, including the widespread use of mobile phones, social media, and increased multitasking, which may contribute to reduced concentration and engagement during traditional lecture-based instruction. (2) In addition, developing a deep understanding of many complex concepts required for effective practice in the medical field remains a challenge. (1) Medical training, with its lengthy years of study, high cognitive demands, and many high-stakes examinations, can lead to high levels of burnout and stress among students. (1) Burnout can have repercussions in terms of poor academic performance, poor recall of information, and mental health struggles. Therefore, there is a strong need for more engaging, motivating, and innovative learning methods within the medical curriculum. (3)

In recent years, the integration of gamification—defined as the application of game design elements in non-game contexts—has emerged as a novel approach to enrich learning experiences in medical education. (4) Gamification leverages elements such as points, badges, leaderboards, and interactive challenges to create an engaging learning environment. The underlying theoretical model, namely, self-determination theory, allows for the student's motivation to arise from three general psychological needs: autonomy, competence, and relatedness. (4) By employing such gaming strategies, educational interventions can maximize intrinsic motivation and, in consequence, learner achievement and engagement. Earlier digital learning tools, including spaced-repetition platforms such as Anki, rapid slide-based quizzes, and interactive polling during lectures, were already used to encourage engagement and reinforce recall. These approaches have been widely studied as effective methods for enhancing active learning and knowledge retention in medical education. (4) Approaches such as competition boards, interactive challenges, point schemes, and immediate feedback have been used to stimulate motivation and improve recall. Over time, some of these have become new models for enriching medical school education. (3) Studies have shown that gamified learning environments can improve participation, foster a sense of achievement, and make complex medical subjects more accessible and enjoyable. (4) All these benefits can be most useful in courses such as pharmacology, pathology, and anatomy, where students must memorize and apply large volumes of information.

Beyond improving engagement, gamification aligns with active learning principles, promoting problem-solving, critical thinking, and collaboration, which are essential skills for future healthcare professionals. (5) In addition, by simulating real-life scenarios, gamification can allow learners to practice in a safe environment where mistakes can occur without risk to patient safety. These platforms can also provide immediate feedback and opportunities for repeated practice, helping students improve their clinical reasoning while incorporating elements of peer competition and still emphasizing mastery of core competencies. This has the potential to bridge the gap between theory and practice. (6) Gamified platforms may also support distance and remote learning environments that became more common following the SARS-CoV-2 pandemic, allowing interactive participation even when traditional in-person instruction is limited and helping facilitate engagement in larger class settings.

In this article, the efficacy of gamification in medical student training in anatomy, pathology, and pharmacology is evaluated, with consideration of both its advantages and limitations. By comparing and contrasting the effectiveness of gamification on student motivation, recall, and academic performance, this discussion aims to shed light on its role in medical training as a potentially revolutionary educational tool.

2 | GAMIFICATION IN ANATOMY EDUCATION

Anatomy is a core part of medical curricula, offering key information about the structure and function of the human body. Nevertheless, its complexity, information overload, and the conventional use of cadaveric dissection can pose challenges to students' motivation, understanding, and information recall. Many students have difficulty in perceiving three-dimensional structures and understanding their spatial relationships, which are essential for clinical application. (7) To counteract such obstacles, instructors have designed gaming tools that create interactive, immersive educational environments, enhancing both effectiveness and motivation in studying anatomical concepts.

One of the most successful gamified approaches in anatomy training is the use of interactive, highly detailed virtual three-dimensional dissection platforms for simulation and research. These platforms allow students to explore anatomical structures in a simulated environment, promoting spatial understanding and long-term retention. (7) Unlike two-dimensional representations in textbooks or conventional cadaver dissection, virtual tools enable learners to manipulate structures, rotate them, and visualize cross-sectional structures dynamically, thereby facilitating hands-on learning. These digital resources are also more accessible and cost-effective than maintaining cadaver laboratories, making them an attractive alternative or supplement for anatomy education. Virtual anatomy platforms and interactive dissection tools have increasingly been adopted in medical education to support spatial learning and student engagement, and similar technologies have been incorporated across medical education settings. (8)

Moro et al. (2017) conducted a comparative analysis between augmented reality (AR), virtual reality (VR), and traditional methods in studying anatomy. (8) In terms of increased knowledge, the analysis found that all three methods were effective; however, students using AR and VR exhibited higher motivation, engagement, and overall satisfaction. The immersive nature of AR and VR technologies enables learners to experience anatomy in ways that more closely mimic real-life clinical scenarios, facilitating the application of theoretical knowledge. Gamification elements such as quizzes, progress tracking, and interactive challenges embedded within these platforms further reinforce learning. For example, students may complete short quiz rounds that award points or badges for correct responses, track their advancement through levels or achievement dashboards as modules are completed, or participate in timed leaderboard challenges that encourage repeated practice and friendly competition among peers. (4)

Apart from AR and VR, gamification in anatomy education can extend to mobile applications and simulation-based games that incorporate competition, rewards, and adaptive study pathways. All such tools enable students to study independently, be given immediate feedback, and engage in personalized study routines, thus leading to a deeper level of complex understanding. For example, case-based approaches allow students to use their anatomical knowledge to bridge the gap between theoretical learning and clinical application. (5)

In general, the use of gamification in anatomical education has significant potential to increase motivation, comprehension, and long-term recall among students. While traditional methodologies will always have a role, gamified tools can serve as strong adjuncts, particularly in overcoming barriers to visualization, interactivity, and motivation.

3 | GAMIFICATION IN PATHOLOGY EDUCATION

Pathology, the study of disease mechanisms and histological patterns, is a critical component of medical education. Traditional pathology training often involves passive study techniques, such as lectures and slide-based review of histological specimens, often presented through PowerPoint discussions or microscopic demonstrations. These methods may not actively engage students, making it difficult to develop the critical thinking skills associated with these topics. Gamified learning activities, in contrast, require learners to apply knowl-

edge through problem-solving tasks, interactive quizzes, or case-based challenges that promote analytical reasoning, improve information recall, and encourage discussion and collaboration among learners. (4) To address these challenges, educators can turn to gamification techniques to create more interactive and stimulating learning experiences.

A particularly striking example is the use of gamification in histopathology training. In a study conducted at Paracelsus Medical University in Salzburg, Austria, Kahoot! was implemented in real-time examination in (histo-)pathology lecture environments. (9) Student performance exhibited a considerable improvement in correct answer proportion—from a mean of 47.2% at baseline to 77.2% post-lecture. There was also a 50% reduction in answer times, indicative of increased efficiency in studying. Student feedback exhibited high acceptance of this gamified format, highlighting its effectiveness in improving learning outcomes in anatomical pathology and morphological topics.

A new and emerging direction in pathology education is the integration of game-based assessments that combine simulation and gamification. Such approaches can enhance pathology education, including student engagement and interest in the subject. As discussed by Shrivastava et al. (2024), such assessments have much potential in enhancing critical thinking and decision-making skills in medical students. (10) Despite discussing the challenges of integration, the authors advocate for a systematic approach to seamlessly integrate these assessments into medical curricula. These approaches may also help prepare students for clinical training and residency by strengthening diagnostic reasoning, decision-making under pressure, and collaborative problem-solving. (10)

The application of VR in pathology training has also been researched to enable immersive learning experiences. For example, Huber et al. (2022) developed a transfusion service laboratory in a VR environment to educate students on immunohematology subjects. (11) The use of educational materials in a virtual laboratory with a gaming environment was effective in engaging students and clarifying complex topics.

Overall, the use of gamification in pathology training can make learning fascinating while also encouraging active participation, critical thinking, and information recall. By transforming traditional passive training methodologies into immersive, participatory experiences, gamified approaches can better prepare medical students for practice in a clinical environment. As technology continues to develop rapidly, new and exciting opportunities for gamification in pathology training will emerge, enhancing students' competency and learning.

4 | GAMIFICATION IN PHARMACOLOGY EDUCATION

Pharmacology, encompassing the study of drug mechanisms, therapeutic applications, and adverse effects, presents a complex and extensive subject matter that many medical students find challenging. To make pharmacology instruction more manageable, instructors have considered numerous approaches to gamify teaching sessions to promote active learning and maximize recall. A quantitative systematic review in 2023 by Hope et al. examined the application of gamification in pharmacology education. (12) The study analyzed 66 articles describing gamified interventions across 12 countries, involving over 8,000 students. The gamified approaches ranged from board games to immersive simulations, with escape rooms being the most frequently reported. The review highlighted the need for improved research quality and better alignment of learning outcomes with these evaluation methods.

In another study, Oestreich and Guy (2022) discussed the role of game-based learning (GBL) in pharmacology education. (13) They noted that GBL, which involves incorporating game elements into non-game activities, can effectively engage students and enhance learning outcomes. GBL was described as leading to long-term student engagement and information recall. The authors also noted the need for more clearly defined assessment methods to evaluate the effectiveness of GBL activities.

Moreover, the review by Hope et al. (2023) further

analyzed the use of gamification in the context of pharmacology. (12) The findings suggested that gamification, when effectively implemented, can enhance student engagement and learning outcomes in pharmacology. However, the study also emphasized the need for rigorous research to establish best practices and ensure that gamified interventions are pedagogically sound and aligned with educational objectives.

5 | CHALLENGES AND CONSIDERATIONS IN IMPLEMENTING GAMIFICATION

While the benefits of gamification in medical education are evident and well-studied, several challenges and considerations must be addressed to ensure its effective implementation. Cognitive overload is one such issue and incorporating gaming elements can distract learners from educational content. De-Marcos et al. (2014) stressed that poorly designed gamified interventions can result in a dip in learning performance through increased cognitive load. (14)

An additional consideration is variation in learner preferences and learning styles. Not all students will necessarily enjoy gamified strategies nor respond effectively to them. Hamari et al. (2016) showed that individual variation, including personality and gaming background, can have an impact on effectiveness of gamification. (2)

Also, the development and deployment of gamified tools require significant investments in funding, time, and technical expertise. Wang et al. (2016) supplemented that successful gamified learning experiences demand significant collaboration between subject matter experts and game designers, which can be resource-intensive. (5)

Competition in specific gamified dimensions can also make learners stressed and nervous, and subsequently, can affect their performance and motivation in a negative manner. In a study conducted by Lester et al. (2023), competition can motivate a group of students but can also have a negative effect, causing them to participate less and perform worse if the circumstances are not optimized. (15)

Moreover, integrating gamification into existing curricula poses logistical challenges. Tabassum (2024) identified issues such as aligning game mechanics with learning objectives, ensuring accessibility for all students, and providing educators with adequate training to effectively facilitate gamified activities. (16)

Despite its potential, careful consideration must be given to such challenges in the context of medical educational gamification. Tailoring gamified interventions to diverse learner needs, ensuring thoughtful design to prevent cognitive overload, and allocating appropriate resources for development and implementation are crucial steps toward successful integration.

6 | FUTURE DIRECTIONS AND RECOMMENDATIONS

The integration of gamification into medical education is an evolving field with significant growth potential. Future studies will need to assess the long-term effectiveness of gamified interventions both in terms of academic performance and their impact on learning in clinical settings. There is a need for uniform frameworks to guide the development and assessment of gamified tools, ensuring consistency and rigour across studies.

Educators are encouraged to adopt a learner-centred approach when implementing gamification, involving students in the development process to better tailor interventions to their needs and preferences. Institutions may also collaborate with technology developers to create high-quality, evidence-based, and objectives-mapped gamified educational tools. Funding opportunities and institutional grants may further support the development of gamification tools in education. Pilot initiatives exploring gamified learning strategies are beginning to emerge in medical education programs, including within Canadian institutions. (4)

7 | CONCLUSION

Gamification has the potential to revolutionize medical training by making learning more engaging, interactive, and effective. In anatomy, pathology, and pharmacology, gamified tools have demonstrated their ability to enhance knowledge retention, critical thinking, and practical application. While challenges exist, strategic implementation and ongoing research can maximize the benefits of gamification, ultimately contributing to the development of competent and motivated medical professionals.

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An Approach To...



APPROACH TO
McGill Journal of Medicine

Approach to: Burn Injuries

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ABSTRACT

Burn injuries are trauma cases with potentially complex pathophysiology and multi-organ considerations, especially in severe cases. Serious sequelae such as compartment syndrome and inhalational injuries must be considered in victims of severe burns. Burn severity is assessed via a combination of burn area and burn depth, using methods such as the rule of nines or the Lund-Browder charts for area and clinical examination to determine depth. Mild burns can be managed on an outpatient basis by family physicians, while major burns should be referred to the local burn center for management. Non-surgical treatment of burns includes dressings, cooling, pain relief, and monitoring for infection, while surgical treatment focuses on the debridement of non-viable tissue and wound closure.

KEYWORDS
Burns, TBSA, Flame, Parkland

1 | QUESTION

A 30 year old male presents to the emergency department for a burn injury. He was pouring accelerant on a small bonfire in his backyard in a semi-enclosed alcove when he slipped and fell into the flames onto his hands and face. He struggled to extract himself for approximately 5-7 seconds and immediately jumped into his pool afterwards to cool down. There was no loss of consciousness. His family called for an ambulance and he was brought immediately to the nearby hospital. The paramedics could not establish an IV access and no fluids were given en route. In the ER, he complains of a mildly sore throat but his main concern is regarding pain control.

On exam, he is alert, oriented and able to speak in full sentences. His blood pressure is 140/90, repiratory rate is 28 per minute, heart rate is 100 beats per minute, and his temperature is 37.0 degress. On inspection he has singed facial hair, facial burns and soot in his orophar-

Abbreviations: TLOC, transient loss of consciousness.

ynx. His burns are circumferential around his arms with weak but palpable pulses distally. The burns on his torso are bright red with sloughed skin and blisters. He decribes extreme pain from the burns on his face and torso, but comments that the burns on his arms "doesn't feel as bad". He has a notable inspiratory stridor but auscultation reveals equal air entry bilaterally. He denies any other past medical history.

A primary survey otherwise reveals no other injuries. What is the most important next step for management of this patient?

A. Establish intravenous access and start Ringer's Lactate to replenish fluids.
B. Assess for inhalational injury via laryngoscopy, with consideration for rapid sequence intubation.
C. Admit to ward to observe burn progression and provide pain control.
D. Perform a bedside escharotomy for the upper extremities.
E. Take a detailed and complete history and calculate the Total Body Surface Area (TBSA) percentage.

2 | ANSWER

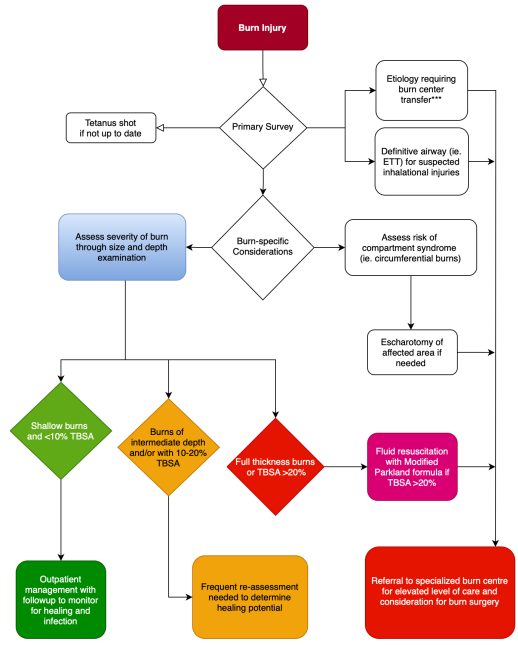
B. Assess for inhalational injury via laryngoscopy, with consideration for rapid sequence intubation.

It is crucial to recognize the signs of a potential inhalational injury based on history and exam findings. Concerning signs can include stridor, voice changes, hemodynamic instability, respiratory distress, and soot/burns in the oropharynx. While the other options presented are valid concerns, it is most important to protect the airway if there are concerns for compromise. Once the airway is secured, further assessment of the burn injury can proceed (i.e., TBSA Calculations, fluid resuscitation, evaluation for compartment syndrome, etc.)

3 | INITIAL APPROACH

Burn injuries should be first and foremost treated as cases of trauma, with the initial attention given to the primary survey to stabilize the patient and reveal other injuries that the medical team need to co-manage. Key components of the trauma survey per the updated 2025 ATLS guidelines include assessment of "xABCDE": eXsanguinating hemorrhage, airway, breathing, circulation, disability, and exposure. (4,6)

Throughout the primary survey, it is important to keep consideration for burn-specific injuries. For the airway assessment, patients should be evaluated for inhalational burns first and formost to rule out impending airway collapse and need for intubation. Studies have shown that inhalational injuries alongside cutaneous burns are associated with significant mortality. (7) Elements of the history/physical exam such as oropharyngeal soot, singed nasal hairs, prolonged exposure to smoke, and being burned in an enclosed space are all risk



FLOWCHART 1 An approach to a patient with burn injuries.

****ABA criteria for etiologies that would benefit from burn center referral includes electrical burns, chemical burns, pediatric cases where the current facility is unsuited for the level of care the patient requires, significant medical comorbidities, or concomitant traumatic injuries. (1)*

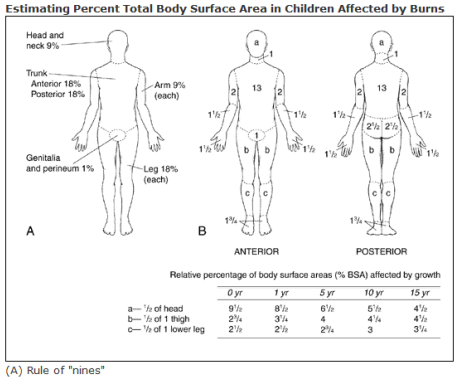
factors for developing airway burns. In 2011, the American Burn Association (ABA) published a set of clinical criteria for intubation in the setting of suspected inhalational injury, including full-thickness facial burns, respiratory distress, stridor, upper airway trauma, swelling on laryngoscopy, altered mentation, hypoxia/hypercarbia, and hemodynamic instability.(8) The airway assessment should also include consideration for cyanide toxicity and/or carbon monoxide (CO) poisoning. CO poisoning secondary to smoke inhalation is of particular concern as standard pulse oximetry cannot differentiate carboxyhemoglobin from oxyhemoglobin.

In addition to inhalational injuries, there are other specific burn etiologies that should prompt consideration for immediate transfer to the local burn center. An example of this includes burns that are electrical or chemical in nature, which can cause complex internal injury requiring specialized care. Cases with concomitant trauma, burns in sensitive locations (i.e., genitalia), pediatric patients in a setting without pediatric-specific care, and patients with significant medical comorbidities are also recommended for transfer. (9)

Lastly, as part of the initial management all burn patients should be offered tetanus prophylaxis if not up to date (within 5 years). Cases of tetanus post-burn injury can be found in the literature spanning more than 100 years, (10) and studies of tetanus immunoglobulin administration have shown good efficacy against the disease. (11)

Once the trauma survey is complete, a more detailed burn-specific assessment can occur. The severity of burns is assessed in two ways: the size/area of the burn and the depth of the burn. Burn depth is divided into superficial epidermal (or first-degree) burns, partial-thickness (second-degree burns), and full-thickness (third-degree) burns. Partial-thickness burns can be further described as superficial and deep-dermal burns (see Table 1). The burn depth is assessed based on appearance and sensation in the area, and is used to predict if the burn requires surgical treatment. In addition to the above classification, the term "fourth-degree burns" is also used to describe devastating burn injuries that extend to structures underneath the dermis such as fascia, muscle, and bone. (12)

Burn area is calculated via "percentage of Total Body Surface Area" (or "% TBSA"). There are multiple ways to estimate burn area, with some common methods such as Lund-Browder charts or the Rule of Nines (see Figure 1). To prevent confusion when communicating burn severity, it is of special note that the TBSA does not include superficial epidermal burns.



(A) Rule of "nines"
(B) Lund-Browder diagram for estimating extent of burns

FIGURE 2 An example of using the rule-of-nines or Lund-Browder charts to estimate TBSA. From the U.S. Department of Health and Human Services, Public domain, via Wikimedia Commons.

A special burn-specific consideration occurs when the patient presents with deep circumferential burns around their limbs or torso, as the resulting non-compliant eschar may lead to compartment syndrome. Classically, the "6 Ps" can be used for assessment of the area: pain, pallor, pulselessness, paresthesias, paralysis, and poikilothermia. If the risk for compartment syndrome is high, escharotomy of the affected area by trained surgical staff should be considered. (14) If the clinical picture is ambiguous, there are tools that can assist the diagnosis of compartment syndrome, including the use of pulse oximetry to assess distal oxygenation, Doppler ultrasound for blood flow, and the direct measurement of compartment pressures using a catheter. (15)

	Superficial Epidermal (First degree)	Superficial dermal (Partial-thickness)	Deep-dermal (Partial-thickness)	Full-thickness (Third degree)
Appearance	Dry and red (often described "like sunburn")	Blisters, red, moist and/or weeping	Blisters, red/white in colour, can be "waxy"	Waxy/leathery white or charred/blackened
Blanchable	Yes	Yes	Sluggish	No
Sensation	Intact, painful to temperature/air/touch	Intact, painful to temperature/air/touch	Painful to touch only	Sensations to deep pressure only
Healing Potential	Will heal over days-week	Will heal with conservative therapy over 2-3 weeks	Usually need 3+ weeks to heal, would likely benefit from surgery	Rarely heals without surgical treatment

TABLE 1 Common attributes of various burn depths. Information in table adapted from Lanham et al. (2), Jeshcke et al. (3), and ABA ABLS course manual (9).

Taking into consideration the size of burn, depth of burn, and the aforementioned risk factors (such as inhalation injuries) will allow categorization of burns into burns that can be conservatively managed as "minor burns" in an outpatient setting, or "major burns" that require assessment by a burn specialist in a specialized treatment facility.

For minor burns, common components of conservative management include pain control, cooling of the area, burn dressings for partial-thickness burns, and frequent follow-up to monitor for healing/infection. (2) Analgesia can often be achieved with oral medication for uncomplicated superficial burns. Cooling the burn with tap water can decrease the tissue damage, decrease pain, and improve healing. Burn dressings allow for an environment that promotes healing with many options including silver-impregnated dressings, honey, and gauze with antibacterial ointments. Blisters may also be kept intact or deroofed to remove a potential nidus for infection depending on area of injury, patient factors, and degree of general clinical concern. Antibiotic prophylaxis is not recommended – a Cochrane review of the subject in 2013 was not able to show a benefit and suggests that it may actually contribute to antibiotic resistance. (16)

For burns of moderate concern that may or may not heal conservatively, frequent follow-up is required to determine healing potential, monitor for developing infections, and prevent heavy scarring/poor cosmesis. The full extent of burns often develop over the course of 48-72 hours, and should be re-assessed at that time to determine a final TBSA and burn depth. (17)

3.1 | Beyond the Initial Approach

For major burns, the large amount of tissue damage causes not only deleterious effects locally at the site of the burn, but also systemically throughout the body. The pathophysiology of large burns includes metabolic derangement, immune dysregulation, as well as large fluid shifts. (3) Large burns have been shown to cause drastic proinflammatory and hypermetabolic states due to dysregulated cytokine and chemokine release. (18) A sustained sympathetic drive can also develop due to the abnormal stress response involving catecholamines and cortisol, while the resulting inflammatory cascade can result in widespread redistribution of fluids, potentially leading to distributive shock and organ failure. (19) This means that patients with large/deep burns often need to be closely monitored in an intensive setting to receive adequate care. This can involve specialist care from intensivists, infectious disease specialists, and anesthesiologists in addition to the burn surgeon. For these cases, scoring systems like the modified Baux score can help prognosticate patients with severe burns, assisting in clinical decision-making. (3)

Due to the loss of the epidermal/dermal layers, there are large amounts of fluid loss through insensible routes that need to be replenished. For patients with a calcu-

lated TBSA of >20%, fluid resuscitation is indicated to combat systemic effects of the burn that lead to large fluid shifts out of the vasculature. There are several different equations to estimate fluid needs post-burn. For example, the modified Parkland formula can be used to estimate the total fluid volume needs in the first 24 hours and is as follows:

$$(2\text{–}4 \text{ mL/kg of Ringer's Lactate}) \times$$
$$(\text{TBSA percentage}) \times (\text{patient weight in kg})$$

This total volume is divided into 2, with one half of the amount given in the first 8 hours, and the second half given in the next 16 hours. (13) The modified Parkland formula serves as a good starting point to estimate fluid needs, but every patient should be evaluated independently for volume status. Notably, the formula is prone to over-estimation and over-fluid resuscitation which carries the risk for fluid creep and volume overload in an already ill patient. The formula should be applied cautiously in conjunction with frequent clinical assessment of volume status (i.e., PoCUS) to prevent fluid overload. A common titration point for adequate fluid resuscitation is a urine output of 30-50cc per hour. (6,12)

In addition to sequelae such as fluid loss, the absence of the skin barrier predisposes patients to infections that can delay wound healing and worsen outcomes. Careful monitoring of the burn sites is required to catch and treat any brewing infectious disease.

Deeper burns often require surgery. The excision of unviable tissue removes breeding grounds for potential pathogens and hastens healing of underlying structures, contributing to decreased morbidity and mortality. (20) Tools like laser doppler imaging, enable the burn surgeon to predict areas that will heal and areas that will not, which can assist in surgical planning for excision and grafting. Once the burned area has been adequately excised, the area can then be closed and allowed to heal. The options for grafting are numerous and are often based on burn severity, patient factors, surgeon preferences, as well as resource constraints. Common grafting options include autografts, allografts (i.e., cadaveric sources), as well as synthetic biomaterials. (3,5) Care for these patients often involves a multidisciplinary team of surgeons, intensivists, internists, specialty nursing, as well as allied health professionals.

3.2 | Conclusion

Burn injuries are traumatic cases that range from extremely simple injuries to complex cases with multi-organ involvement. Burn severity is assessed via a combination of burn area and burn depth. Minor cases can be managed on an outpatient basis by family physicians, while cases of concern should be referred to the local burn center.

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Reflection



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Loco-Regional Anesthesia: Building on the Past to Solve Tomorrow's Challenges

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For most, anesthesia is often solely perceived as putting patients to sleep and waking them up shortly after. It encompasses much more than that.

Medicine progresses through continuous improvement, with new technologies and medications building on previous innovations. What may seem obvious today was a revolution yesterday. There are always new challenges to tackle. Improving pain management remains a priority, specifically the balance between increasing efficacy and mitigating the inherent risks of intervention.

KEYWORDS
Local Anesthesia, Regional Anesthesia, Medical History, Opioid Crisis, Medical Innovation

0.1 | A brief history on the evolution of regional anesthesia: Targeting medication where it counts

The fundamental triad of anesthesia comprises three primary components: unconsciousness, muscle relaxation, and analgesia. This short essay will explore the latter through the advent of anesthesia restricted to specific anatomic regions (termed loco-regional anesthesia), ensuring pain management without the risks of general anesthesia.

As an alternative to general anesthesia, some procedures can be managed with local or regional anesthetic interventions where the patient stays awake, but pain is managed by numbing the relevant region. Such techniques allow for reduced risks associated with ventilation and hemodynamic control, especially in patients with preexisting concomitant medical conditions such as pulmonary or heart diseases. Endotracheal intubation also presents a risk to the respiratory tract, but also to the musculoskeletal system as seen in patients with

rheumatoid arthritis who are at increased risk for cervical injuries.

By the end of the 19th century, the benefits and risks of general anesthesia using ether had been well established following the first public demonstration by the dentist William T. G. Morton in Boston, Massachusetts, in 1846.(1)

In this context in 1884, ophthalmologist Carl Koller and colleagues, were experimenting with several substances at the Vienna General Hospital, looking for a viable alternative to general anesthesia that would ensure pain control during ophthalmologic surgeries while limiting risks. Through experimentation with animals, he eventually stumbled upon cocaine.(2)

Cocaine is extracted from the leaves of the coca plant. Native to the forests of South America, it was imported to Europe by an 1859 Austrian expedition.(2) Peruvian and Bolivian indigenous communities were aware of coca's euphoric properties from chewing its leaves.(3) In the mid-1800s, European explorers and scientists grew increasingly curious about its psychotropic effects and were soon experimenting on it by extracting its active chemical compound – cocaine.(3,4)

The first recorded successful attempt at local anesthesia was performed by Koller in 1884, when he self-administered drops of cocaine into his eyes and took note of its local anesthetic properties after surgical manipulation on himself. (5)

Following Koller's self-experimentation, the value and ease of local anesthesia rapidly gained global recognition. Other physicians and surgeons quickly shared new anesthesia techniques using cocaine. One such surgeon was William Stewart Halsted in New York City. Through experimentation on himself, fellow physicians, and students, he discovered and described the nerve block that resulted from injecting cocaine into the trunk of a sensory nerve.(6) Unfortunately, Halsted's experiments led to a dependency on cocaine. His addiction later forced him out of New York City's medical scene and into a new chapter as a teacher and founding figure of the newly formed Johns Hopkins University Medical School.

A few months later, in 1885, once again in New York City, a neurologist mistakenly injected cocaine too far into a patient's back and likely became the first to perform a spinal block.

Years later, in 1898, Einrich Quincke devised the theory of the spinal block, which involved guiding a needle through the skin, the subcutaneous tissues, between the vertebrae, and the dura before reaching the subarachnoid space. Once in place, a local anesthetic, cocaine, would be injected to provide temporary anesthesia starting at that spinal level and below. This technique was then performed in August of 1898 by August Karl Gustav Bier, a German surgeon, on his assistant.(7)

The field of regional anesthesia was further developed in 1921 when Fidel Pagés, a Spanish military surgeon, developed epidural anesthesia. In his paper, "Anesthesia metamérica", Pagés described a technique similar to the spinal block, but without perforating the dura.(8) His epidural technique allowed long-acting anesthesia at a specific level of the spine by placing a catheter in the epidural space and continuously pumping an anesthetic solution.(9)

As with any scientific discovery, epidural anesthesia was made possible by building on earlier discoveries and innovative techniques now forgotten by history. Unfortunately, credit is not always given to the pioneers but is instead given to those who publish or speak out the loudest. Such was perhaps the case of Vassily von Anrep, a Russian doctor who may have been the first to use cocaine as a local anesthetic in 1880 before Carl Koller's first recorded attempt in 1884. Von Anrep's techniques and results were published in Russian and outside of mainstream scientific journals and he was therefore forgotten.(2,10)

Nevertheless, the advent of loco-regional anesthesia in all its forms has opened a new chapter and is still widely used in medicine today. The epidural anesthesia technique is a secure and effective method for pain management. While it requires technical skills, the insertion of a catheter across the ligamentum flavum allows the administration of an anesthetic – nowadays usually bupivacaine, ropivacaine, or solutions of those anesthetic agents mixed with other drugs – into the epidural space, thereby achieving regional anesthesia. A

well-executed epidural block reduces the need for general anesthesia, airway management, and postoperative opioid use. It has also been associated with lower pain scores, shorter postoperative hospital stays, and fewer complications.(11)

0.2 | Tackling the public health challenge of dependency

Today, loco-regional anesthesia is still making progress with the development of additional techniques and new delivery systems. However, one problem persists. Anesthesia is effective for the period during which an anesthetic solution is given, but what happens once the anesthesia wears off? The patient's pain begins. For several decades, opioids have been the only available ambulatory treatment for postoperative pain. While they are effective analgesics, they are also very addictive drugs.

In Canada, the increase in opioid prescriptions over the last few decades has played a significant role in opioid overuse. Many factors have also contributed to the increase of opioid consumption, including increased use of illegal opioid drugs and increased potency of opioid substances, such as Fentanyl and Carfentanil, outpacing the use of other less potent opioids. All the while, prescription drugs remain a major driver of opioid usage. Consequently, many patients have developed opioid dependence, contributing to the current opioid crisis.

According to the 2018 Canadian Community Health Survey, opioid prescriptions and long-term opioid therapies are decreasing.(12) Still, approximately 12.7% of Canadians were estimated to be using opioids that same year.(12) From the end of the 1990s to 2020, opioid overdose deaths increased four to fivefold in both Canada and the United States.(13,14) The Centers for Disease Control and Prevention (CDC) reports that 21% of those deaths involved prescription opioids.(13)

Although tackling the opioid crisis extends far beyond what goes on in operating rooms and chronic pain management clinics, finding an alternative to oral opioids could help alleviate the current crisis. Fortunately, new developments in modern loco-regional anesthesia may provide such an alternative in the management of postoperative and chronic pain. New drug combinations such as dexamethasone (a long-acting corticosteroid) or dexmedetomidine (a selective alpha-2 adrenoceptor agonist with vasoconstriction and anesthetic properties) combined with local anesthetics could provide patients with longer-lasting local analgesia.(15) Furthermore, innovative techniques of peripheral nerve blocks for ambulatory patients following upper or lower extremities surgeries (16) have also decreased the need for postoperative opioids. These techniques include different approaches to brachial plexus blocks alongside several regional anesthesia options for the lower extremities including lumbar plexus, psoas compartment, or femoral nerve blocks.(16) Therefore, exposure to these addictive medications could either be delayed or prevented.

By building on previous discoveries, continuously improving techniques, and searching for alternatives to current anesthetic options, new frontiers in anesthesia may hold promising tools to tackle the serious medical and public health challenge of the opioid crisis. Building on the past may hold insights to tackle one of medicine's key challenges: pain management.

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From Pain Relief to Perioperative Physicians: How Anesthesiologists Transformed Surgical Care Through Humanism

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ABSTRACT

The evolution of anesthesiology as a medical specialty reflects a continuous humanistic commitment to relieve suffering, preserve dignity, and protect patients from avoidable harm. In the preanesthetic era, surgical care was defined by extreme pain, limited precision, and high mortality. The introduction of ether anesthesia in 1846 made pain preventable and transformed surgery into a more controlled and humane practice. As procedures grew more complex, anesthesiologists' role expanded from inducing unconsciousness to preventing physiologic harm through airway management, monitoring, and balanced anesthesia. That same patient-safety ethic broadened their responsibilities across the surgical journey: from preoperative risk assessment and optimization to postoperative recovery, surveillance, and critical care—thus cementing anesthesiologists today as the perioperative physicians. Beyond surgery, this humanistic mission also shaped the role of anesthesiology in chronic pain medicine and palliative care, where relieving suffering and preserving dignity remain central goals. Together, these developments show that anesthesiology is not merely technical support for surgery, but a humanistic discipline grounded in patient advocacy and safety across the continuum of care

KEYWORDS
Anesthesiology, Humanism, Perioperative Medicine, Patient-Centered Care

Surgery in the preanesthetic era was a brutal experience. Patients were awake, restrained, and screaming in unimaginable agony. (1) The introduction of ether anesthesia in 1846 changed medicine forever—not just by conquering pain, but by allowing surgery to be a controlled, precise, and humane practice. Since then, anesthesiologists' roles have expanded beyond merely facilitating unconsciousness into preoperative optimization, intraoperative management, and postoperative recovery. They became true perioperative physicians—ensuring that patients not only survived surgery, but also were optimized, protected, and healed.

This evolution was not accidental. Like its origins in pain relief, the development of anesthesiology was driven by its fundamental philosophy that undergoing surgery is a human experience that demands caring for the whole patient. Humanism in medicine, as defined by Dr. George Thibault, is a system "in which human interests, values, and dignity predominate". (2) In the context of this paper, a humanistic practice of medicine means not only treating disease, but also recognizing suffering, preserving dignity, and protecting vulnerable patients. The role transformation of the anesthesiologist into the comprehensive perioperative physician proves that anesthesiology has never been just a technical speciality, but one deeply rooted in humanism, patient advocacy, and a commitment to patient safety.

0.1 | Anesthesia Eliminated Pain: The First Humanistic Revolution in Surgery

The advent of anesthesia eliminated the excruciating pain that had long defined surgery, reframing it as a patient-centred discipline focused on survival and comfort. Although modern anesthesiology is usually traced through Western figures such as Morton and Snow, ancient Chinese, Indian, and Arabic traditions also made efforts to reduce pain and suffering, reflecting a broader human impulse that long precedes modern anesthesia. (3) Before anesthesia, surgery was considered a last resort. (3) Patients endured illness until they chose between surgery or death. Nineteenth century playwright Frances Burney described her mastectomy: "cutting through veins, arteries—flesh—nerves … [My] scream lasted unremittingly … I almost marvel that it rings not in my Ears still!" (1) Surgeons also suffered, often "[vomiting] after their patients' forced torment." (4) Moreover, the pain and blood loss limited surgical precision. (5) Surgical success and patient survival depended on speed, as exemplified by Robert Liston, referred to as "the fastest knife in the West End", who completed amputations in as little as 28 seconds. (1, 5, 6)

In 1846, Dr. William Morton's public demonstration of ether anesthesia at Massachusetts General Hospital marked the birth of modern anesthesia. (7, 8) Morton, a young dentist, sought a safe and effective alternative after seeing the failure of nitrous oxide as an anesthetic. As he witnessed the effectiveness of inhaled ether in tooth extractions, he demonstrated that general surgery, too, could be performed painlessly. While ether was far from a perfect anesthetic, it shattered the belief that pain during surgery was inevitable. Anesthesia transformed surgery from a desperate, crude practice into a more precise and outcome-driven discipline. (4) But Morton's demonstration was more than a scientific breakthrough; for the first time, the patient's experience of undergoing surgery was recognized as a concern to be addressed through medical innovation. Pain was no longer inevitable, but rather something to be prevented during surgery. Anesthesia marked medicine's first step toward humanistic surgery.

Anesthesia also reshaped societal attitudes toward pain relief. (8) While patients perceived early anesthesia to be "the epitome of humanitarianism," (7) some medical and religious communities regarded it as immoral, arguing that pain during surgery and childbirth was natural and necessary. (4, 7, 8) Dr. John Snow challenged these ingrained beliefs, by successfully administering chloroform during Queen Victoria's childbirth in 1853. (5) Her endorsement inspired others to seek pain relief during procedures, promoting the perception that patient dignity and comfort should be addressed in medicine.

0.2 | From Pain Control to Life-Saving Intraoperative Specialists

As surgeries became longer and more complex, anesthesiologists faced the new challenge of keeping unconscious patients alive and safe through the physiological stresses of surgery. Driven by the same humanistic philosophy, anesthesiologists evolved from pain relievers into intraoperative specialists, managing vital functions of the human body to maximize patients' chances of survival.

A key milestone occurred when Dr. William Macewen pioneered endotracheal intubation in 1879, preventing airway obstruction and suffocation, a major cause of perioperative mortality at the time. (8) This "secure airway" laid the foundation for modern airway management, ensuring safe ventilation for patients under general anesthesia. (9) In 1902, Dr. Harvey Cushing introduced hemodynamic monitoring. (10) He found that stabilizing blood pressure through a regional injection of cocaine before major amputations prevented shock and death, demonstrating the critical role of autonomic stability in patient survival. These innovations made surgery into controlled, predictable procedures with improved survival rates. (11)

A Canadian breakthrough further transformed the field in 1942, when Dr. Harold Griffith of Montréal introduced the first neuromuscular blocker, curare. (8, 12, 13) Before curare, muscle spasms constantly challenged abdominal surgeries and could only be overcome by excessive anesthesia, causing dangerous metabolic disturbances. (14) Muscle relaxation through curare enabled balanced anesthesia, allowing surgeons to safely perform complex procedures like open-heart and neurosurgery while reducing anesthesia-related complications. (11) Griffith's discovery exemplified the humanistic spirit, commitment to patient safety, and compassion that drove innovations in anesthesiology. (13, 15)

With advancements in airway management, hemodynamic stability, and muscle relaxation, many surgical fatalities became preventable. (11) A growing expertise in physiology and pharmacology helped establish anesthesiology as a specialty of its own, defined by its mission to enable surgical success while ensuring patient safety and survival. Anesthesiologists—once perceived as mere technicians—became the guardians of life during surgery, skillfully balancing unconsciousness, vital organ function, and the demands of surgery. This protective role is itself a uniquely humanistic act: once anesthetized, the patient is completely vulnerable and unable to advocate for themselves. In medicine where patient autonomy is a central ethical principle, anesthesiology is unusual in requiring patients to temporarily give up that autonomy, entrusting their safety and bodily functions to the hands of the anesthesiologist. Few moments in medicine involve such complete surrender of autonomy. This transfer of responsibility gives routine anesthetic care a distinctly humanistic character, rooted in a profound trust between the patient and the physician. Paradoxically, this role often takes place quietly, as some of the anesthesiologist's most important acts of advocacy occur while the patient is unconscious and unable to witness them.

0.3 | The Birth of the Perioperative Physician: Caring for the Whole Patient

With these life-saving advancements in the theatre, anesthesiology made surgery tolerable to patients of all ages and conditions, including the weak and elderly. (8) Yet, this humanistic mission did not stop within the theatre; anesthesiologists expanded their responsibility to encompass the entire surgical experience. They introduced proactive preparation and effective recovery methods to further improve patient outcomes, guiding patients through every stage of surgery to heal from illness. (16)

Recognizing that conditions like anemia and cardiopulmonary disease led to poorer surgical outcomes, anesthesiologists developed the preoperative evaluation to assess whether patients had sufficient physiological reserve to withstand anesthesia and surgical stress. (17) In 1941, the American Society of Anesthesiologists (ASA) introduced the ASA Physical Status Classification System, the first risk stratification tool in medicine. (17, 18) This system evaluated a patient's health before

surgery, helping anesthesiologists predict complications and tailor perioperative management to each patient. This preoperative evaluation placed a strong emphasis on patient safety, and had a profound impact on the organization and efficiency of the surgical system. (17) Building on this foundation, anesthesiologists then introduced prehabilitation—a proactive approach that empowers high-risk patients to improve their physical fitness, nutrition, and emotional resilience before surgery begins. (19) Beyond medical optimization, prehabilitation recognizes the connection between daily lifestyle and physical and mental health, helping patients enter surgery stronger and better prepared. Prehabilitation teams often consider patients' social barriers to surgical recovery in their care plans, such as limited transportation, inadequate caregiving support, or unstable housing, further demonstrating the broader role of an anesthesiologist as a health advocate. This holistic approach reflects the patient-centered philosophy of perioperative medicine—that patients are individuals with physical and emotional needs to be addressed to maximize recovery. (20)

Post-operatively, patients initially faced pain, respiratory failure, and life-threatening complications. (11) Committed to reducing suffering and improving safety, anesthesiologists developed dedicated recovery units equipped with resuscitation tools and staffed by trained nurses under their supervision. (21, 22) A major JAMA study in 1947 revealed that nearly half of post-operative deaths were preventable, highlighting the need for vigilant monitoring and early interventions. (22, 23) These recovery areas evolved into modern-day Post-Anesthesia Care Units (PACUs), where patients are now continuously monitored during the critical recovery period immediately after surgery, significantly reducing postoperative mortality. (22)

Early recovery areas were also the origins of modern Intensive Care Units (ICUs). The concept of critical care emerged during the 1952 polio epidemic in Copenhagen. Seeing polio patients suffer from respiratory failure, anesthesiologist Dr. Bjorn Ibsen applied techniques used for his critically ill post-operative patients, such as intubation and mechanical ventilation, to the care of polio patients. (24) His innovative approach reduced the poliomyelitis mortality rate from 80 percent to 40 percent. (25) Inspired by this success, Ibsen transformed a recovery room into the first ICU, where any patient needing ventilation and hemodynamic monitoring would receive appropriate care in a dedicated area. (25) With their expertise in airway management and organ support, anesthesiologists naturally became leaders in critical care, improving survival rates of their patients perioperatively and beyond. (24)

These perioperative developments laid the foundations for Enhanced Recovery After Surgery (ERAS) guidelines in the 2000s, a holistic approach designed to optimize the entire surgical experience, from preoperative prehabilitation to postoperative strategies. (26) Aimed for smoother and faster recovery, implementation of ERAS guidelines has been shown to reduce hospital length of stay and perioperative morbidity while increasing patient satisfaction. (26) ERAS represents the culmination of decades of advancements in perioperative medicine, reinforcing that surgery is no longer solely about survival, but about safety, positive patient outcomes, and a smooth recovery. As architects of perioperative medicine, anesthesiologists have consistently combined expertise and compassion to push the boundaries in surgical care, shaping the patient-centred approach that defines modern surgery today.

0.4 | Anesthesiologists Beyond Surgery: Continuing the Humanistic Mission

Beginning with pain control and intraoperative care, the innate humanistic approach of anesthesiologists naturally cemented their unique role as perioperative physicians. Yet, anesthesiology did not evolve around the needs of surgery alone. With their broad expertise and skillset in relieving suffering, managing complex symptoms, and caring for vulnerable patients, the same humanistic philosophy led anesthesiologists into adjacent fields, such as chronic pain and palliative care.

In chronic pain medicine, pain is recognized as not only a physiological and sensory signal but also an emotional lived experience shaped by biological, psycholog-

ical, and social forces—explaining why chronic pain can be profoundly disabling even when structural findings are subtle or absent. (27) In contrast to acute perioperative care, chronic pain medicine takes a longitudinal approach that prioritizes function, coping, and quality of life alongside symptom reduction. (28) Within multidisciplinary pain programs, anesthesiologists contribute pharmacologic expertise and procedural skill, using multimodal strategies such as rehabilitation, psychological supports, and interventional therapies when appropriate, while balancing symptom relief with the long-term risks of medications and interventions. (28, 29) This work reflects the same humanistic principle that shaped anesthesiology from its beginnings: taking suffering seriously and advocating for patient-centred care. (29)

A similar humanistic philosophy connects anesthesiology to palliative care, where the goal shifts from curative treatment to comfort, dignity, and relief of suffering. Palliative care is defined as an approach that improves quality of life for patients facing life-threatening illnesses by preventing and relieving physical, psychosocial, and spiritual suffering. (30) In this context, anesthesiologists contribute expertise in symptom management, including careful titration of analgesics and other medications to relieve pain, dyspnea, and anxiety while respecting patients' goals and values. (31) By focusing on comfort, communication, and dignity, palliative care reflects the broader role of anesthesiologists as patient advocates in the most vulnerable moments of illness.

0.5 | Conclusion

Today, anesthesiologists are seen across the hospital: in the operating rooms, prehabilitation clinics, ICUs, pain clinics, and even palliative care wards. Their widespread presence and leadership across different settings reflects their commitment not just to understand diseases or master techniques, but to deliver compassionate and patient-centred care throughout the entire patient journey. Anesthesiology stands as a testament to the very essence of medicine—the aim being not just to cure diseases, but to safeguard humanity through every breath, every heartbeat, and every vulnerable moment.

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