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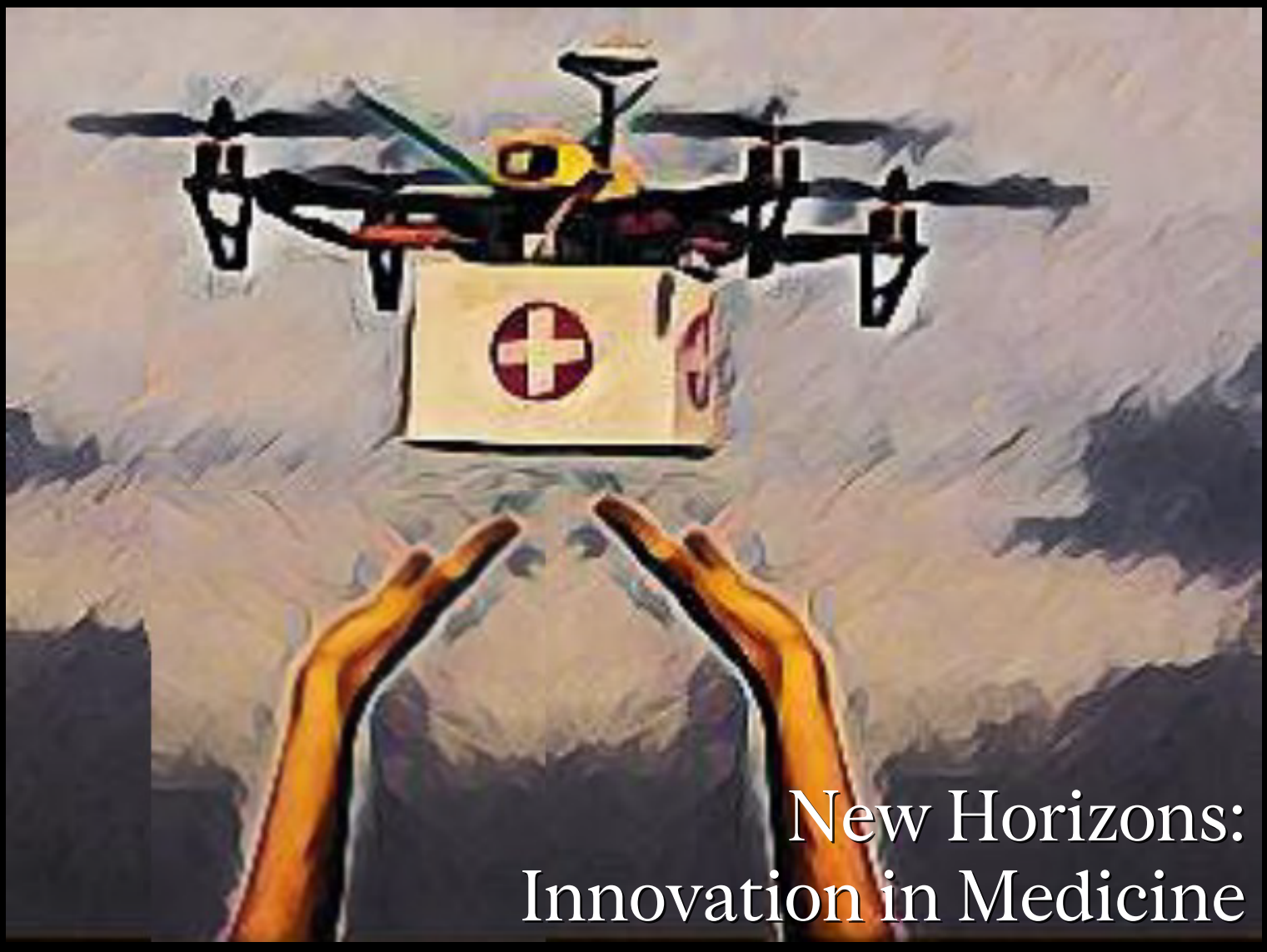

New Horizons: Innovation in Medicine

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MJM Volume 20, Issue No.2, September 2022

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Letter from the Editors: The Winds of Scholarly Change

The McGill Journal of Medicine (MJM) is pleased to present the second issue of our 20th volume, *New Horizons: Innovation in Medicine*, our annual issue composed of various types of articles involving new methods and ideas in the fields of healthcare and research. Innovation in medicine is particularly relevant during these trying times, as many have identified a need to transform and reinvent aspects of healthcare systems with more effective and efficient technologies and protocols. Furthermore, the COVID-19 pandemic was a sobering reminder of the perpetual need to rethink and optimize processes within and across our medical institutions. Today, over two years since its onset, we continue to deal with the aftereffects of the pandemic, as we attempt to harness our new knowledge to improve the systems currently in place.

This issue highlights the insight and knowledge we continue to hone in the face of uncertainty and adversity, with articles related to COVID-19 and quality improvement, amongst other interesting topics. This issue also features several *Approach To* articles, which were introduced in a standalone issue of MJM's 19th volume. These articles continue to promote the mastery of managing common clinical presentations and associated resource stewardship in clinical practice. They are particularly useful for our readers in early stages of their medical education, providing perspective and insight into clinical algorithms for diagnosis and treatment.

Over the past year, we were pleased to see continued growth in the volume of submissions to MJM, and as a result, the steady rise in output of our journal. We hope to increase the number of original research papers in the issues that follow and welcome submissions from authors in diverse fields. Our initiatives outside of traditional editorial publications, including our online workshops and podcast series, have gained traction and interest from international audiences. In the coming year, we hope to present new and valuable concepts in both domains to our readers.

To close, we would like to thank all members of our various units for their continued hard work in maintaining our peer-review, publication, and media pipelines to the highest of standards. We also thank our contributors, reviewers, and readership for their unwavering commitment to and support of MJM. We look forward to the following year in expanding our initiatives to drive publication goals forward and setting the foundation for the journal to flourish and evolve in future years.

Sincerely,

Stefanie Perrier
Co-Editor-in-Chief, McGill Journal of Medicine
PhD Candidate

Bennet Desormeau, MSc.
Co-Editor-in-Chief, McGill Journal of Medicine
MD Candidate

Mack Michell-Robinson, MSc.
Executive Editor, McGill Journal of Medicine
MD-PhD Candidate

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Foreword:
Dr. Roland Grad

The research articles, narrative reviews, case reports, commentaries, reflections, and approaches to clinical topics showcased in this issue of the journal were a joy to read. These contributions were submitted under a theme of *New Horizons: Innovation in Medicine*. But what do we mean by innovations in medicine? Being new is not of itself innovative. Innovation requires evidence of impact, but putting on my skeptical hat, how can impact be quantified? The debate around the value of journal impact factors or alternative metrics of scholarly activity is one example of the complexity of measuring impact.

Coincidentally, I recently noticed the images on our 100-dollar bill. These include a DNA strand, insulin, and an ECG tracing – all notable Canadian contributions to medical research under the theme of "Medical Innovation". Putting aside any feelings of patriotism, I admit that as a practicing family doctor, I was most attracted to the following contributions in this issue - in no particular order.

In their narrative review, *Teymourlouei* assessed the effectiveness of exercise in preventing hamstring injury in soccer players. Of the six trials they included in this review, three reported a marked reduction in injury, two found a modest reduction and a sixth reported no clear effect of the intervention. Given the degree of variation in the type of exercise tested in these trials, no meta-analysis was conducted.

From Pakistan comes a review of the effect of CMV infection in women of childbearing age. While the seroprevalence of CMV is associated with the socioeconomic status of the affected area, apparently 40 per cent of pregnant women in Canada will have IgG antibodies indicative of past infection. While CMV can reactivate, in Canada we presently test only symptomatic persons, and not routinely in the first trimester.

A narrative review examined the impact of the pandemic on the mental health of post-secondary students. The sudden transition to online learning exposed young adults to loneliness, leading some into a state of despair. Among young adults with no prior mental health problems, in cross-sectional studies, increased symptoms of grief, depression, anxiety, and PTSD were noted. Has the institutional obligation to monitor and provide outreach and counselling services ever been greater?

Huerne provides insight into the complexities of direct-to-consumer genetic testing, a service that has captured the interest of consumers (and several of my patients). Interestingly, in fine print, companies such as *23andMe* explain how their tests are not intended to reveal a person's state of health, determine carrier status, or assess the risk of developing a certain disease. Questioning the science as well as the ethics of direct-to-consumer genetic testing, it exposes the limitations of this technology for predicting individual disease risk or ancestral background.

Given the associations between infectious disease and cardiovascular disease, *Shokoples, Ferreira and Comeau* review how the SARS-CoV-2 virus interacts with the cardiovascular system, describe why patients with cardiovascular disease are at an increased risk of succumbing to COVID-19, and discuss the long-term cardiovascular implications of the pandemic.

Not to take a shot at my alma mater, but I learned nothing about foot pain in medical school. *Modarresi and Modarresi* remind us of the strong correlation between the propensity to report pain of somatic origin (such as foot pain) and the state of our patient's mental health. This points to the importance of going beyond the biomedical model - our patients benefit when we implement a biopsychosocial model of care.

Medical education benefits from innovative learning strategies. One such strategy, called retrieval practice, can optimize the retention of long-term memory. Given the volume of information presented to medical students, you will enjoy the commentary by *Risk and colleagues* if you are curious about methods to improve memory. These authors smartly propose the need to apply experimental methods to evaluate the impact of learning strategies. While randomized trials of educational interventions are important to demonstrate what works and for whom, they are not easy to do.

Cheng and colleagues reflect on how to improve health equity through knowledge sharing with the public. One consideration is to enhance the medical school curriculum for developing communication skills in the context of an increasingly multicultural society. As the pandemic showed us, another challenge is that of improving communication with people who have low levels of health literacy.

Bouhadana and Sadri provide medical students with a stepwise approach to the diagnosis and management of lower urinary tract symptoms (LUTS). But in the presence of obstructive symptoms in older men, should the family physician pursue a diagnosis of prostate cancer? If the patient has no family history of prostate cancer and the digital rectal exam is normal, the decision to request a PSA test to look for prostate cancer seems to diverge from the patients' reason for visiting the doctor in the first place. LUTS are not predictive of aggressive prostate cancer, so what is needed is a discussion with patients about the harms versus benefits of PSA testing in this context.(1)

Dhoot and Wan provide a clear description of how to test your patient for strabismus, which can result in vision loss due to amblyopia. The US Preventive Services Task Force recommends clinicians screen children aged 3-5 years at least once to detect strabismus.

I wonder how the circumstances of the pandemic influenced student authors. For example, did social distancing and lockdown afford some extra opportunity to develop new skills, or just to read and write? So, I asked the medical students I worked with over the past two years. Their responses varied – and I can see no clear benefit on scholarly activity associated with this pandemic.

That said, I thought I would close as follows: "*Whenever you might think that the world as you perceive it will soon disappear, always remember that the actual situation is better than you think.*" (2) These words opened a review of the McGill Journal of Medicine 25 years ago in the New England Journal of Medicine. May they guide and comfort us through the next 25.

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ORIGINAL RESEARCH

Artist: Morgane LeBerre

ORIGINAL RESEARCH
McGill Journal of Medicine

Sonoist: An Innovative Peer Ultrasound Learning Initiative on Canadian Teaching Hospital Wards

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ABSTRACT

Background: Students usually learn point-of-care ultrasound (PoCUS) on standardized patients, thus lacking opportunities to correlate their ultrasound findings with clinical abnormalities. Sonoist is a student-led initiative aimed at improving ultrasound training with peer-teaching and real patients. We describe here a pilot project of Sonoist, its implementation and evaluation.

Methods: Sonoist was developed by Independent-Practitioner certified medical students who teach their peers how to scan patients with abnormal clinical findings, then correlate their ultrasound findings with the physical examination. From May 2019 to February 2020, seven sessions were held, with a sessional average of 3 participants and 3 patients scanned. We collected survey data on ultrasound knowledge, participants' perceived self-improvement, and general comments. Results were grouped by prior ultrasound training (novice n=8, experienced n=12) and year of study (1-4).

Results: 20/23 completed the survey. An increase in ultrasound skill was perceived by all of novices and 67% of experienced learners. Knowledge about clinical indications for PoCUS improved in 80% of novice and 81% of experienced students; sonographic knowledge improved in 69% of novices and 81% of experienced learners. All novices and 92% of experienced learners reported that learning ultrasound was useful for correlating with physical exam and clinical diagnosis. All novices and 83% of experienced students preferred peer-to-peer teaching.

Conclusion: Peer-to-peer PoCUS teaching improved medical students' sonographic and clinical knowledge and was perceived as useful by students. A combination of early clinical exposure and a less stressful environment from peer teaching may contribute to these results.

KEYWORDS

PoCUS, Medical education, Ultrasound, Peer teaching

1 | INTRODUCTION

Point-of-Care Ultrasound (PoCUS) is a preferred bedside imaging method in many clinical situations. It is quick to perform, easily accessible, non-invasive, and without radiation exposure. As PoCUS is used in an increasing number of medical specialties, its incorporation into medical schools' curricula is growing.

One barrier to faculty teaching is a lack of staff who have expertise in PoCUS and time to do additional teaching outside of regular clinical duties. (1) Peer teaching, the process of using experienced students as teachers for their peers or near peers, can address this gap. Peer-teachers and their students share similar experiences and language, and have similar social roles, which promotes comfort and decreases stress. Yu et al. have shown that peer-teaching for PoCUS in undergraduate medical programs is comparable to conventional staff-teaching. (2)

Currently, undergraduate bedside ultrasound curricula focus on practicing scans with standardized patients. Scanning healthy models provides technical skills but leaves trainees with a lack of exposure to actual abnormalities and little knowledge about clinical indications to perform the scans. In addition, learning in a non-clinical setting does not encompass workplace learning, whereas interactions with patients provide informal feedback cues that allow for ongoing improvement. (3)

Sonoist is a near-peer ultrasound innovation run by medical students addressing the lack of clinical exposure in current ultrasound curricula. During Sonoist sessions, medical students scan in-patients with ultrasound-detectable findings while being taught by their Independent-Practitioner (IP) certified peers. Learners have the opportunity to correlate their ultrasound pathologies with patients' presenting symptoms, medical history, and physical exam findings.

Given the need for appropriate ultrasound training, the effectiveness of peer teaching, and the lack of clinical and pathological exposure in current PoCUS curriculum, we hypothesize that introducing programs like Sonoist early in clinical training will increase ultrasound knowledge, skill, and understanding of pathological findings. The present study describes a pilot of the Sonoist initiative, its implementation, and evaluation.

2 | METHODS

2.1 | Participants

McGill University medical students from first to fourth (final) year participated. From the students who signed up, 3-4 were selected as participants for each session on a first-come first-serve basis; this maximized scanning time while considering patient comfort. Those who signed up for multiple sessions but were not previously selected were given priority. Learners were asked to prepare by reviewing introductory video resources found on the Sonoist website (https://www.sonoist.com/) that explain the basics of each scan.

2.2 | Setting

The sessions took place in university-affiliated teaching hospitals' internal medicine wards or coronary care units (CCU), each equipped with a portable ultrasound machine. The attending physicians or senior residents on service were contacted for permission; they also offered a list of patients with potential ultrasound detectable abnormalities. The instructors met each patient prior to being scanned to obtain consent. All patients agreed to participate and were aware of the educational nature of the session.

2.3 | Implementation of Sonoist

The Sonoist initiative was created by IP-certified medical students. IP is a certification provided by the Canadian Point of Care Ultrasound Society to perform, document, and teach point of care ultrasound across Canada. From May 2019 to February 2020, seven peer-taught ultrasound sessions were held, lasting 2 hours each. Because of the in-person and hands-on nature of the sessions, they had to be paused since the start of the COVID-19 pandemic. Scans taught included eFAST (free fluid), intrauterine pregnancy, lung and pneumoth-

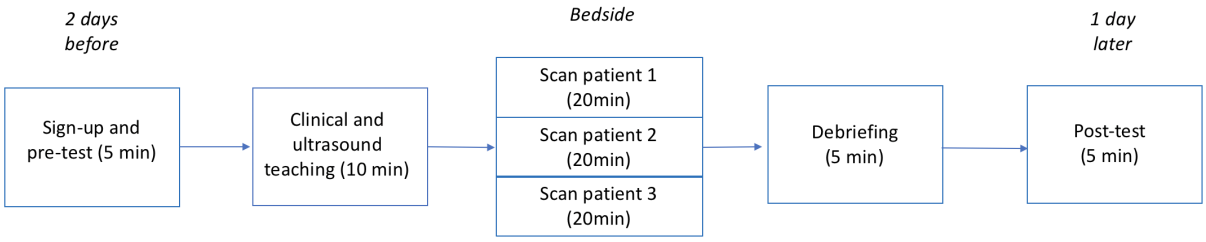

FIGURE 1 Structure of a Sonoist session.

orax, gallbladder, subxiphoid view of the heart and advanced cardiac views. Learners were asked to prepare for each session by reviewing scans found on the Sonoist website.

IP instructors and student participants reviewed the scans again together prior to the session (Figure 1). The group then went to the bedside and elicited a brief history. A focused physical exam was performed. Each student then practiced the indicated scan for each patient. Finally, the group debriefed by discussing the differential diagnosis, emphasizing how bedside ultrasound guided their thought process.

2.4 | Program Evaluation

Pre- and post-online Google surveys collected data on the participants' ultrasound and clinical knowledge, subjective and objective improvement, and feedback about the sessions (Table 1). The survey was adapted from other similar near-peer evaluations. (4) Questions assessed both clinical knowledge, such as indications to use PoCUS, and technical ultrasound knowledge, such as specific ultrasound findings related to a pathology. Results were de-identified and grouped by level of ultrasound training. The survey results were analyzed with descriptive statistics and two-tailed T-tests were used to determine statistical significance.

Consent to participate in the study was obtained from each participant who was made aware that the survey results were intended for research purposes. Names were only collected for the pre-intervention survey as identification was required to sign up. After the initial data was collected, they were de-identified by removing their names. Later, surveys were sent to participants via individualized URLs in order to link it with their pre-survey. During the entire process, the data remained confidential by being only available to the student researchers and not shared with any other potential clinical evaluator. Participants were free to opt out of the survey with no repercussions.

3 | RESULTS

23 students participated in an ultrasound session, of whom 87% (20/23) completed both a pre-test and a post-test survey. The majority were either in their second (9/20) or third (8/20) year of study. 12/20 participants had some experience, defined as previous sessions in ultrasound, and these were mostly in third year. 40% of participants were beginners, most of them being second year students with no formal training in ultrasound. Most attendees (20/23) were present for a single Sonoist session.

3.1 | Subjective Skill Improvement

In response to the question "did your ultrasound technique improve," all eight beginners reported subjective improvement, whereas 8/12 experienced participants did. Following the session, novices reported that they were much improved (4.6/5), whereas the experienced group described moderate improvement (3.8/5).

Analyzing by year yielded similar results. Students with the most experience, third years, stated subjective moderate average improvement (3.6 of 5), with only half stating they improved at all. All preclinical students, first and second years, subjectively thought they improved

	In Pre-test Survey	In Post-test Survey	Scale
Demographics			
What is your level of ultrasound?	x	x	1-5
What is your year of study?	x	x	Free text
Subjective assessment			
Did your technique of ultrasound improve?		x	1-5
Was PoCUS useful to incorporate in the physical exam?		x	1-5
Was seeing PoCUS-detectable pathologies useful in your clinical diagnosis?		x	1-5
Was PoCUS useful clinically?		x	1-5
Was peer-teaching helpful?		x	1-5
Would you prefer peer-to-peer teaching or staff teaching sessions?		x	Peer vs. staff
Will you advocate, or wish to use, PoCUS for your future exams?		x	1-5
Did PoCUS help narrow your differential?		x	1-5
Objective assessment			
Sonographic knowledge: 1. What does 3 B-lines in one intercostal space suggest? 2. How can we differentiate a gallstone from a cyst?	x	x	Multiple choice
Clinical indications: 1. Which imaging modality is superior to pick up pleural effusion? 2. Which of the following is a clinical indication for PoCUS?	x	x	Multiple choice

TABLE 1 Pre- and post-intervention survey sent to participants. Surveys consist of 4 parts: self-assessment, demographic data, subjective assessment and objective assessment of intervention.

much more: first years subjectively improved on average 4.5 of 5 (n=2); second years improved on average 4.4 out of 5 (n=9).

Self-reported improvement pre- and post-intervention yielded similar results (Figure 2). Beginners self-reported a difference in 28% of skill, with significant results ($p<0.05$). Experienced users only noted an 8% increase in skill ($p<0.05$).

Students in their earlier years of training, such as those in their first year of medical school, showed the largest change of 30%, which decreased as the years went up: 16% and 13% for years 2 and 3 accordingly. No result was significant when analyzed by year.

3.2 | Objective Improvement

Figure 3 shows the change in both clinical and ultrasonographic knowledge. When assessing clinical knowledge, beginners showed an increase of 31% and 44% in clinical indications and sonographic knowledge respectively. Experienced users showed an increase in 25% and 33% in clinical indications and sonographic knowledge.

First year students showed a 50% increase in clinical indication and 50% in technical sonographic knowledge; second years showed a 55% increase in clinical indication and 61% in technical ultrasound knowledge; and third years showed a 25% increase in clinical indication and 37% in actual ultrasound knowledge.

3.3 | Physical Exam with PoCUS

All beginners reported that the use of ultrasound was better than physical exam alone, with an average score of 4.8 of 5 when answering the question "was PoCUS useful to incorporate in the physical exam?". 92% of experienced users stated that it was useful, with a score of 4.4 of 5. With this, all beginners stated that there was utility in narrowing the differential diagnosis using ultrasound, especially for pathognomonic findings, with a score of 4.9 of 5. All experienced users stated similarly,

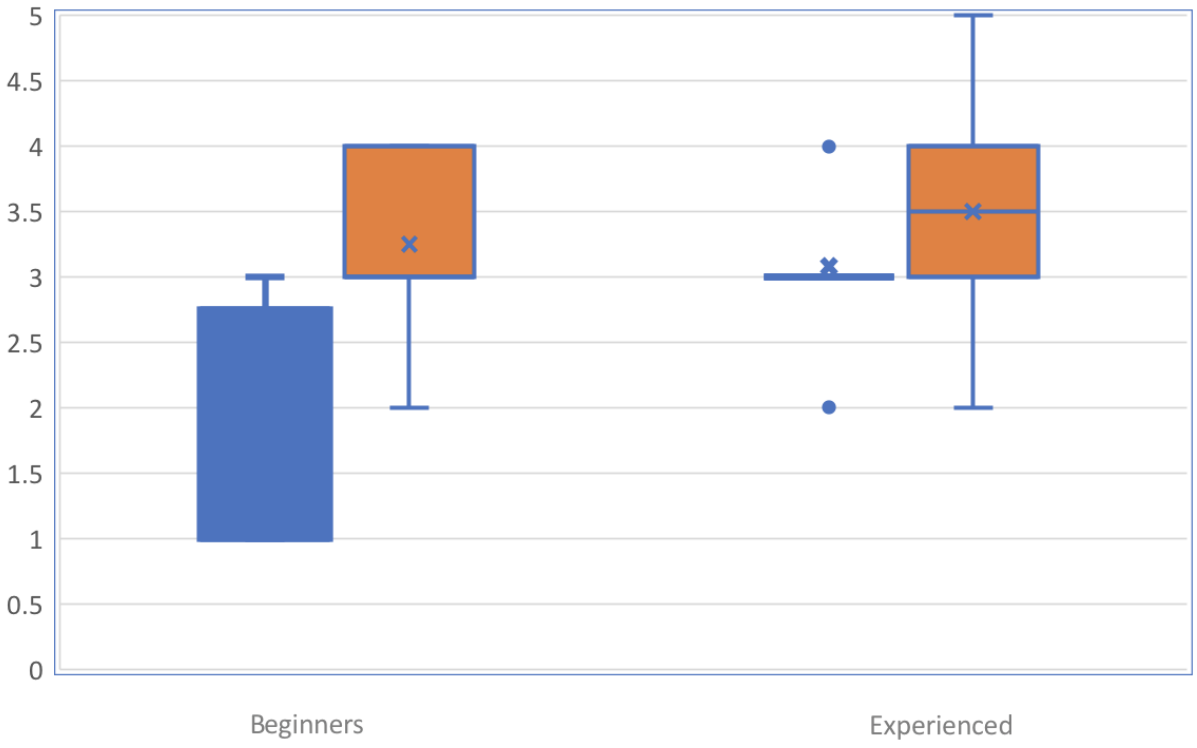

FIGURE 2 Self-perception of skill pre- and post-intervention.
Blue is pre. Orange is post.

with a score of 4.8 of 5.

All participants, except two students from second year, suggested that ultrasound was a necessary adjunct for the physical exam. Only one (1/9) second year stated it was not necessarily useful, though the average usefulness for clinical use and narrowing the differential was highest in this group at 4.9 of 5.

3.4 | Utility and Peer Teaching

All users (20/20) reported that the sessions were useful and agreed that ultrasound would likely be used in the future, as well as advocate for its use in clinical scenarios where appropriate.

With regards to peer-to-peer teaching, all novices, as well as those in first and second year, preferred student-led sessions, whereas 83% (10/12) of experienced users did. Of those in their third year, 8/9 preferred student sessions and 0/1 in fourth year did.

4 | DISCUSSION

We report the first use of combining teaching through patients with real clinical findings and peer-to-peer ultrasound as a means to increase ultrasonographic and clinical knowledge. An increase in ultrasound knowledge and subjective skill were observed in both beginners and experienced learners, though most significantly in self-identified beginners. The positive effects of ultrasound noted in the literature, such as an increase in clinical indication and pathological identification, were similarly noted. Moreover, learners of all levels stated their preference for peer-to-peer teaching over staff teaching.

The benefits of peer teaching are well known: it provides a comfortable learning environment for students, allows peer-instructors to consolidate their knowledge through teaching and use less medical education resources to achieve comparable results. (5, 6) This is the first published study, however, to show its use on

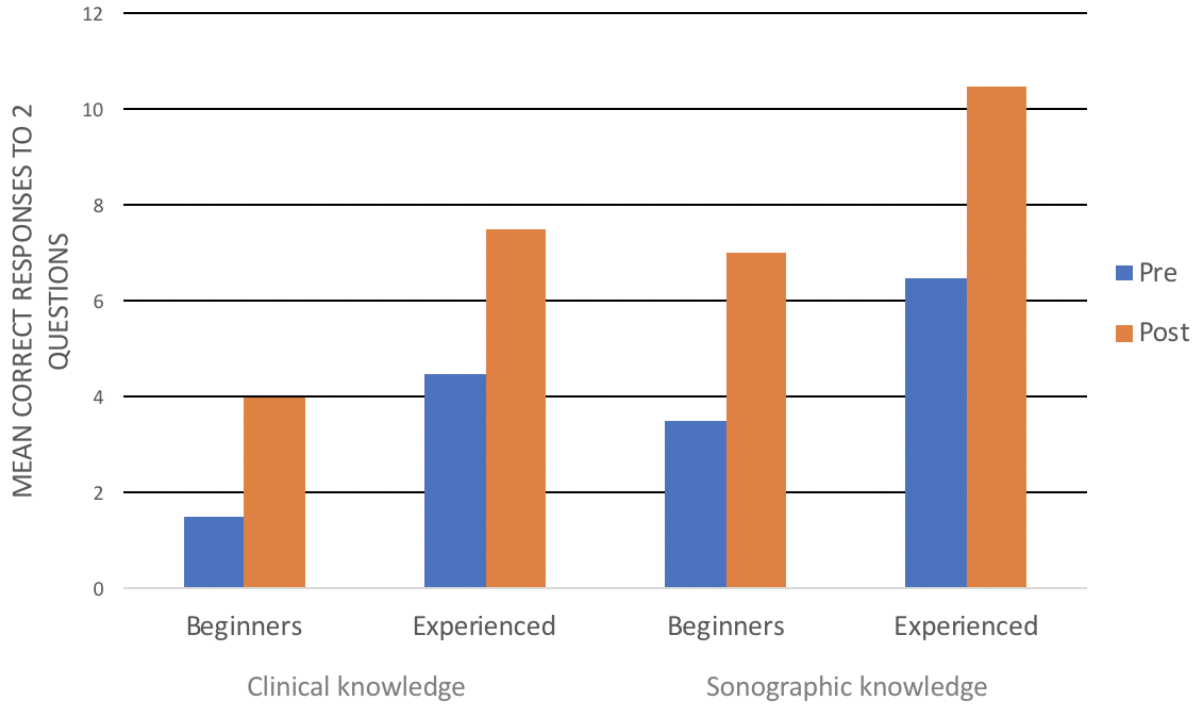

FIGURE 3 Mean correct answers to questions evaluating ultrasonographic and clinical knowledge pre- and post-Sonoist session.

Total of 20 surveyed participants at Canadian hospital wards over 7 sessions. Blue is pre. Orange is post.

real patients with positive ultrasound findings. Although benefits were observed in all groups, they differed in their perception of gains. For example, experienced users perceived that they improved much less than their objective scores suggested. Beginners, however, believed they improved more proportionally to their objective scores. The latter could be explained by learners equipped with less knowledge having lower expectations of their improvement compared to more advanced learners. Providing early exposure in a low-stress environment, therefore, may be key in ensuring greater perceived benefits and self-confidence for students in ultrasound.

Similarly, preclinical students in their first or second year of study showed the largest subjective perceived improvement with a mirrored increase in their quantitative measures. This suggests the presence of a steeper learning curve in the initial phase of ultrasound education. Such a trend is not uncommon in medical education, where it has often been noted that pre-clinical exposure maximizes learning for beginning medical practitioners. (7)

The increased clinical and ultrasound knowledge might further be explained by workplace learning concepts, where learners feel they are included in actual hospital work. (3) Many transitional clerkship curricula attempt to mirror this learning by exposing pre-clerkship students to authentic clinical settings. (7) As more schools foster early clinical exposure, it is likely ultrasound curricula will need to incorporate projects like Sonoist to mirror actual sonographic work.

There are limitations in this study. Because the project was brought to a halt since the start of the COVID-19 pandemic, it was conducted only at two sites with a few patients and pathologies; however, we feel that the patients' pathologies generally represent what a medical student might see at a typical teaching hospital.

Additionally, though the majority of the feedback received from each session was positive, there are key questions remaining. What are other contexts in which peer-teaching is preferred over staff teaching? What would be the effect of using peer-instructors with less training? Previous PoCUS initiatives noted that different levels of effective instructorship relied on their comfort with both the technical and clinical aspects of ultrasound. (3) Novice instructors may require further training to ensure excellence in teaching, and to properly identify clinical findings. Further work will go into creating a skill-based assessment of students and instructors who are being observed and graded undertaking POCUS.

Importantly, most participants preferred peer clinical teaching. Possible reasons include low stress roles without significant responsibility, comfortable learning environments, and the ability to have first on-hand exposure. Thus, Sonoist is a promising initiative that addresses the need for qualified faculty by putting students at the forefront of innovation. Such student exposure and teaching may be increasingly necessary, with ultrasound seen as a future "fifth pillar of physical examination". (8)

Peer-to-peer teaching like Sonoist improves sonographic, clinical knowledge of both experienced and beginner PoCUS practitioners, increases perceived benefit and advocacy for PoCUS, and is preferred over other staff teaching in this specific context. It is a helpful tool that requires further investigation on learning strategies and styles but offers a promising future.

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ORIGINAL RESEARCH
McGill Journal of Medicine

Can an Emergency Surgery Scheduling Software Improve Residents' Time Management and Quality of Life?

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ABSTRACT

Background: Operating room efficiency is invaluable. Particularly in public health systems, where resources are limited and patient loads are high, efficient systems underpin the continued delivery of high quality care. In addition to impacting patients, the implementation of efficient healthcare tools has the potential to improve staff quality of life. In the face of growing surgical resident attrition and healthcare worker burnout, developments in standard practice, such as the implementation of the 80-hour work week, are necessary to improve quality of life.

Materials and Methods: A new online scheduling software (ORNET.CA) was created, installed, and piloted in a Level I Trauma Center after instructing users (physicians and nurses) on its use. A 20-item survey was then distributed to all users to assess the effect implementation of the software had on their quality of life.

Results: ORnet was shown to improve communication between hospital staff and physicians, reduce workflow interruptions, and improve the quality of the working environment. The survey showed that 60% of residents and 50% of attending staff believed that ORNET.CA improved their quality of life.

Conclusions: We present data from a novel emergency operating room scheduling system that allowed surgical residents and attending physicians to better plan their on-call shifts. Staff (resident and physician) reported survey results suggest that implementation of this system resulted in an improved quality of life and a decrease in stress and anxiety levels.

KEYWORDS

Quality of life, Operating room scheduling, Surgical residency, Operating room management

1 | INTRODUCTION

The regular day to day activities of residents in surgical specialities are very demanding. Studies examining all operating room staff show that residents have more work burden, longer work hours, more physical work, and high levels of stress. (1-5) In one study, the majority of surgical residents noted that they experience work-related stress that is moderate to severe. (5) These residents also reported to be drowsy during the daytime and that the stress affected their overall well-being. (5)

The higher stress situation that surgical residents go through partly explains higher burnout rates among surgical residents. (2) Multiple studies have looked at the reasons for this, and in one study, future lifestyle, sleep deprivation, and work hours were the main reasons residents decided to quit residency. (1) The higher attrition rates amongst surgical residents also affects work quality, personal and family problems and in turn affects patient care. (5) Solutions attempting to decrease attrition rates in surgical programs have included: allowing for post call days, decreasing maximum number of work hours, and providing diverse support methods for residents throughout their residency. However, some studies report negative outcomes even after the implementation of these methods. (6, 7) In addition, little or no literature exists on methods to improve time management for residents, particularly during on-call duties.

Being a surgical resident in Canada differs from the United States because of less operating room (OR) resources in a Governmental Health Care system. (8) In Canada, emergency non-elective cases are more likely take place during evening and weekends since operating room resources are limited; non-elective surgery is typically limited to one operating room per institution in Canada and performed only once elective cases during the day have all been completed. (9, 10) Therefore, all surgical specialities struggle to get their emergency non-elective cases done while only one OR room is running. Rarely would two services be operating at the same time in two different rooms unless a life-or-death situation exists. Hence, cases being done later in the evening or night become more common. (9)

In this paper, we present a novel software implemented and used in a Level I Trauma Center intended to improve communication and allow residents to better predict the emergency room operating room schedule and in turn improve time management and quality of life.

2 | METHODS

A new online scheduling software ORNET.CA (Montreal, Canada) was created and installed in a Level I Trauma Center (test site). All nursing staff were trained for its use. Physicians were also sent an email with instructions on its use. The software was launched in October 2015. The software depicts the operating room (OR) schedule on weeknights or evenings (emergency non-elective OR time). OR nursing staff input the list of emergency non-elective cases for the day in real-time based on priority classification levels established by the health care center using it. On-call physicians then log in to the web based real-time scheduling software and view when their case would start and if the start time has been advanced or delayed due to other emergency cases being completed or booked. In a situation where an OR is delayed due to emergency, the physicians on-call are notified immediately via e-mail/text message notification or via the web-based scheduling software directly. Information about scheduled cases, start times, and equipment needed is visible to the health care professionals in real time.

A short online survey was emailed to all 133 users (from the departments of orthopaedic surgery, general surgery, and plastic surgery) in April 2018 to determine quality of life measures and effects of the software on its users. This survey consisted of 20-items and was designed in English (Appendix A) for surgical physicians working at the Montreal General Hospital (MGH). Respondents were given a 1-month time frame to answer the survey, which inquired about the usability of the software and its effects on time management and quality of life. A request to participate in this online survey was sent to all the surgical residents and attending surgery staff at the site electronically, including a link to

anonymously complete the questionnaire. Descriptive statistics using Microsoft Excel 2019 were used to analyze the survey results. Responses were analyzed and grouped based on answer likelihood.

No patient information was present on the scheduling software to ensure patient confidentiality. Only procedure, expected surgical time, and surgical department was shown on the scheduling software. This allowed for communication of start times, surgical equipment requirements for each case, and allowed for real-time case flow management without compromising patient privacy.

3 | RESULTS

A total of 133 surveys were sent out, with 68 respondents representing a 51% response rate. However, 20 responses were not completed and were excluded from our analysis. 30 surgical residents and 18 surgical staff (36.1% of total surveys) fully completed the survey and their results were analyzed. While the 36.1% final-inclusion response rate is low, the authors judge that the survey was likely answered primarily by the physicians who used it most often. Senior residents were more likely to respond to the survey as they are on OR call more frequently than their junior colleagues. This population would thereby have the hand-on experience required to judge the effect of the software on quality of life, and return an accurate overview of the software's impact. 67% of included physicians responded that they use ORNET.CA very often or often (more than 6 times/month) during their on-call shifts, with all other physicians reporting occasional use of the software (3-5 times/month). 93% of residents used the software regularly to determine when a case was scheduled to start. In addition, 83% of residents believed ORNET.CA improved communication and reduced the number of phone calls to the OR by at least 25-50% in comparison to prior to the software being implemented. Half the attending physicians also responded similarly.

3.1 | Time Management

When asked if ORNET.CA helped improve time management, 80% of residents (Figure 1.) and 44% of attending physicians agreed or strongly agreed. In addition, 68% of residents (Figure 2.) and 39% of attending physicians agreed that ORNET.CA helped plan their evenings and weekends while on-call to engage in wellness activities, complete errands, and plan their study time more efficiently.

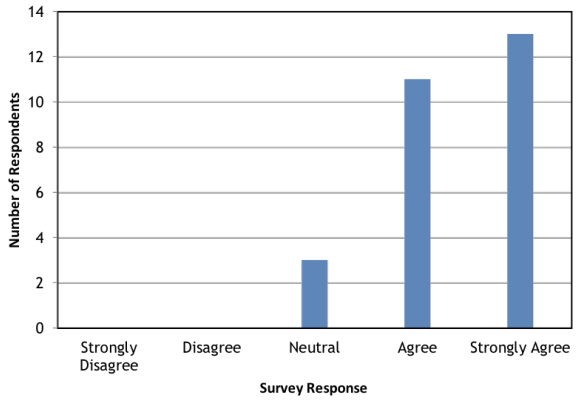

FIGURE 1 Resident Survey Results: ORnet is useful to help manage your time during your on-call shifts

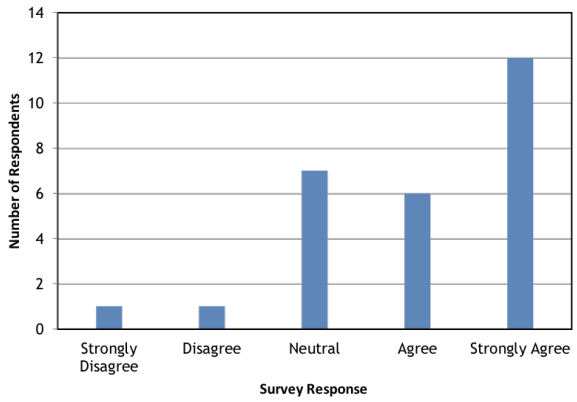

FIGURE 2 Resident Survey Results: ORnet has helped plan your evenings/weekend on-call to engage in wellness activities or errands

3.2 | Quality of Life

When asked if ORNET.CA helps reduce anxiety and stress while on-call, 47% of residents agreed or strongly agreed (Figure 3.), whereas only 22% of attending staff agreed or strongly agreed. In addition, 60% of residents (Figure 4.) and 50% of attending staff believed that ORNET.CA improved their quality of life.

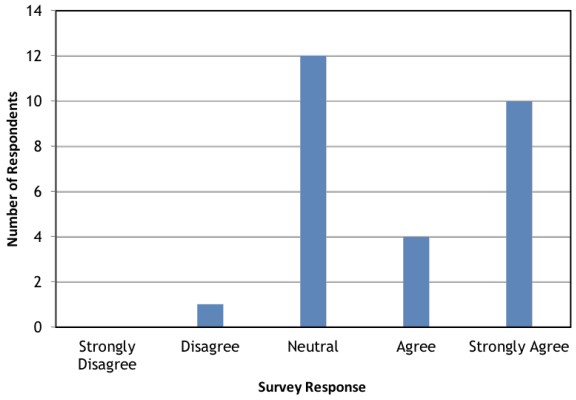

FIGURE 3 Resident Survey Results: ORnet has helped reduced stress/anxiety during on-call shifts

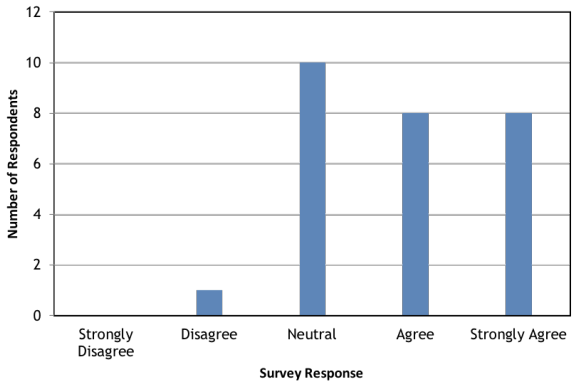

FIGURE 4 Resident Survey Results: ORnet has helped improve quality of life

3.3 | Time Management Communication and Usefulness

The majority of residents (67%) and 39% of attending physicians believed that the software improves communication between nurses and physicians in the OR. Additionally, 56% of attending physicians and 73% of residents believed that ORNET.CA is useful and should be continued to be used for emergency OR scheduling. Although recently adopted and launched as a pilot project at the MGH, the majority of users find ORNET.CA useful, improving communication and quality of life for those using it.

4 | DISCUSSION

This paper presents a new real-time scheduling software with visual depiction of cases on the emergency list used in a Level 1 Trauma Center in Canada and investigates its ability in improving communication between operating room staff and its ability to improve physician and resident quality of life. As demonstrated by the results of an online survey, this simple solution allowed for physicians and residents to better predict their on-call duties and in turn help them rest when possible or engage in wellness activities.

Surgical residents' well-being and attrition rates have become an important topic for discussion over the past few years. (1-7, 11) With high surgical resident attrition rates in the United States and Canada, research has focused on reasons for the high drop-off rates. The literature consistently showed that long working hours, (1) future career lifestyle,(1, 11) and sleep deprivation to be common reasons for residents to not complete their residency training. (1) With attrition rates as high as 17%, (11) workload and environment have been questioned. Therefore, resident well-being has become important for all surgical programs. In this paper, we present data that shows that a simple scheduling software allowed residents to better plan their time while on-call, which contributed to improved quality of life. Our results also found that the software program was able to decrease stress levels and anxiety, which have been linked to resident burnout. (5)

Solutions to minimize surgical resident attrition have been investigated in the United states. (6, 7) Some studies have shown that strategies such as work hour restric-

tion and post-call days have decreased residents' time in the hospital but has consequently negatively affected patient care and resident education. (6) Many studies demonstrate that resident stress is high and related to work hours, (1, 4) but limited studies have investigated the effect of stress related to unpredictable work hours and inability to schedule activities while on-call. Here we present a novel method for physicians, residents, and other hospital personnel to better predict their on-call shifts. This new software allows for residents to verify in real-time when their case will be expected to start and verify as frequently as they would like to in the matter of seconds rather than spending minutes to call the OR charge nurse. Therefore, they are able to better predict if they have time to have dinner, get some sleep, plan a basic life task such a grocery shopping, or schedule study time. We believe that taking away some of the unpredictability helps reduce their stress and improve quality of life as shown in the survey results.

Although the software used here was implemented for use by all OR personnel, the survey demonstrates that its effect in decreasing anxiety/stress levels and improving quality of life was more impactful for residents compared to attending staff. This is consistent with the literature that shows the likelihood of burnout due to stress is higher in residents than other OR personnel, including nurses. (3) This can be related to the fact that other operating room staff have fixed shift schedules while residents have more variability in their work hours and highly unpredictable on-call shifts. In addition, in most circumstances, residents are more frequently on-call than attending physicians. Hence, the use of the software presented here allows for better predictability and allows for stress reduction amongst residents as shown in the survey results.

One limitation of this study is that the results are taken from the experience of one center in Canada. (12) Other centers may report different perspectives on the use of the software, especially in the United States where more resources are available and emergency non-elective OR time is less scarce. (12) In addition, our survey results stem from a small number of surgical residents at the a single tertiary care center. Future studies will look at the use of the software in more centers, including community centers, and determine if differences exist. (12)

5 | CONCLUSION

Here we present data from a survey after the use of a novel emergency operating room schedule implemented in a level trauma center in Canada. The results show that a simple visual scheduling software allows surgical residents and attending physicians to better predict their on-call shifts. The results also show that a simple scheduling software accessible to all allows for improvement in quality of life and a decrease in stress and anxiety levels amongst residents. This in turn could potentially equate to a reduction in attrition rates among surgical residents.

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RESEARCH ARTICLE
McGill Journal of Medicine

Thrombolytic Administration for Acute Ischemic Stroke: What Processes can be Optimized?

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ABSTRACT

Background: The therapeutic benefit of tissue plasminogen activator (tPA) for acute ischemic stroke is proven but extremely time-dependent. Currently, guidelines recommend a < 60 minute door-to-needle time. We identify here factors affecting door-to-needle time of tPA administration for acute ischemic stroke.

Methods: We conducted a retrospective chart review of an emergency department from 2010 to 2013. Inclusion criteria were discharge diagnosis of acute ischemic stroke and tPA administration within 4.5 hours of onset. Exclusion criteria were non-ischemic strokes (transient ischemic attacks, subarachnoid hemorrhage, intracerebral hemorrhage) or those given tPA > 4.5 hours. We used a linear regression model to quantify factor influence and compared tPA administration benchmark times to target benchmark times (median + quartiles).

Results: Among the 71 ischemic stroke patients included, 38 (54%) received tPA within ≤ 60 minutes. Female sex was associated with a door-to-needle time delay of 13.97 minutes (95% CI 3.412 to 27.111). Median benchmark times did not show evidence of delay in any benchmark in comparison with target benchmark times.

Conclusion: Female sex was associated with increased door-to-needle time. Further investigation of these areas may enable optimized workflow, decreased door-to-needle times, and improved patient outcomes.

KEYWORDS
Stroke, Thrombolysis, Emergency department, Workflow

1 | INTRODUCTION

Acute ischemic stroke is the leading cause of disability and the fifth leading cause of death in the United States (1). Intravenous (IV) recombinant tissue plasminogen activator (tPA) as a treatment for acute ischemic stroke has a Class I, Group A level of evidence recommendation from the American Heart Association/American Stroke Association (AHA / ASA) guidelines (2). The therapeutic benefit of tPA is proven but extremely time-dependent. Pooled data from large randomized clinical trials have shown that the therapeutic benefit declines throughout the first 4.5 hours after symptom onset, after which there is no benefit (3, 4). Additionally, it has been shown that each 15-minute reduction in tPA administration time causes the gain of an average equivalent of 1 month of disability-free life (5).

Because of the clear time-dependent benefits of tPA, (AHA / ASA) guidelines on acute ischemic stroke treatment state that the tPA door-to-needle time should be within 60 minutes (2, 6-8). The door-to-needle time is defined as the time from hospital arrival until tPA administration. Additionally, the Target: Stroke initiative outlines more benchmark times, such as door-to-CT (computed tomography) within 25 minutes and door-to-coagulation labs within 45 minutes (6-8). While methods such as advanced pre-hospital notification and acute stroke triage pathways have been shown to decrease door-to-needle time (9-11), best practices are not implemented in many hospitals throughout in the United States (12) and two-thirds of acute ischemic stroke patients still have door-to-needle times over 60 minutes (13). Therefore, further research is required to elucidate factors delaying tPA treatment. The objective of this study is to identify patient factors and workflow steps that are associated with delays in administration of IV tPA in patients presenting with acute ischemic stroke.

2 | METHODS

We conducted a retrospective chart review of patients presenting to an inner-city county emergency department (ED) in the United States from June 2010 to May 2013. All patient data was taken from this hospital's "Get With The Guidelines-Stroke" database, and authors verified patient datapoints and timestamps through individual chart review. Patient inclusion criteria were a discharge diagnosis of acute ischemic stroke and administration of IV tPA within 4.5 hours of symptom onset. Exclusion criteria included patients presenting with intracranial hemorrhage, subarachnoid hemorrhage, a transient ischemic attack, or patients who were given IV tPA after 4.5 hours. tPA after 4.5 hours was used as an exclusion criterion to better identify problems in the tPA administration process for the vast majority of cases, rather than outlier cases for whom the tPA workflow process may not be as widely applicable. Selection of patients is described via Figure 1.

We collected patient demographic factors, clinical factors, and tPA administration timed benchmarks to study their effect on primary and secondary outcomes. Patient demographic factors included age, race/ethnicity, and sex. Clinical factors included method of arrival, onset to arrival time, systolic and diastolic blood pressure, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and co-morbidity. We studied 11 tPA administration timed benchmarks based on the "Target: Stroke" initiative: 1) triage done ($\leq$ 1 min); 2) stroke alert paged ($\leq$ 5 min); 3) patient to critical care room ($\leq$ 5 min); 4) emergency physician at bedside ($\leq$ 5 min); 5) neurologist at bedside ($\leq$ 15 min); 6) blood carried to lab ($\leq$ 15 min); 7) head CT performed ($\leq$ 25 min); 8) verbal results of head CT available ($\leq$ 45 min); 9) head CT results in electronic medical record (EMR) ($\leq$ 45 min); 10) complete blood count (CBC), prothrombin time/international normalized ratio/partial thromboplastin time (PT/INR/PTT) results in EMR ($\leq$ 45 min); and 11) tPA ordered ($\leq$ 50 min).

Our primary outcome was door-to-needle time of tPA administration. Data on pre-hospital notification and other secondary outcomes, such as disposition location, were available only for a limited number of patients and therefore were not included in our analysis. Likewise, other limitations (see discussion) prevented analy-

sis of additional secondary outcomes such as in-hospital mortality, ambulation at end of day, ambulation at discharge, and hospital length of stay.

This study was consistent with established methodologic recommendations (14, 15) and was approved by the Baylor College of Medicine Institutional Review Board, which granted a waiver of informed consent for our retrospective analysis.

2.1 | Data Analysis

Door-to-needle time was defined as a categorical variable with two groups: 0-60 minutes (no delay) and 61-270 minutes (delayed administration). We calculated descriptive demographic statistics and standardized mean difference to measure the effect of each feature on whether a patient would have delayed tPA administration.

We built a simple linear regression model to quantify the influence of each patient demographic and clinical factor on door-to-needle time, a continuous response variable. The estimated effect was calculated to determine each variable's impact on door-to-needle time in number of minutes.

Finally, we compared the time for the completion of 11 tPA administration benchmarks in our data to target times set by the AHA / ASA (6) (a benchmark time greater than the AHA / ASA target time would constitute a delay). Benchmark times are reported using minutes and median + quartiles.

Data was analyzed using RStudio version 1.1 (RStudio Inc., Boston, MA).

3 | RESULTS

Patient selection is shown in Figure 1 and demographic and clinical factors are shown for each door-to-needle time group in Table 1. Of 1,181 patients presenting with symptoms of stroke during the study time period of 2010 - 2013, 71 (6.0%) met the inclusion criteria. Of these, 38 (54%) received tPA within ≤ 60 min, while 33 (46%) had a delayed door-to-needle time. Our tPA pop-

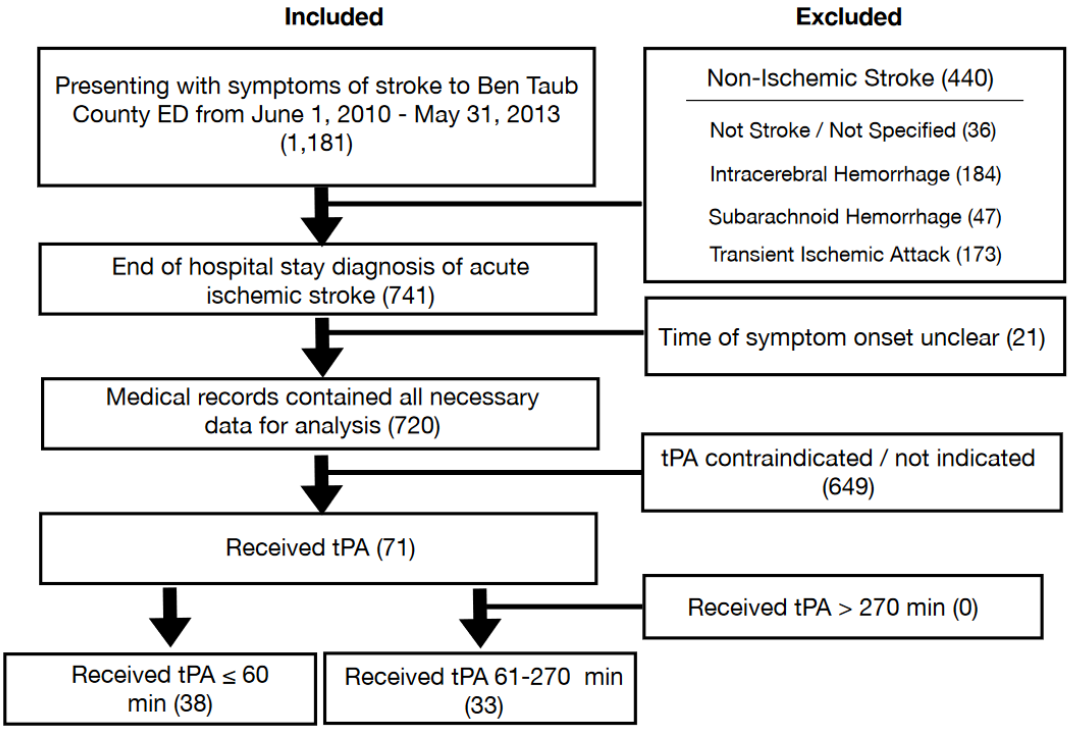

FIGURE 1 Selection of patients

ulation was 49% male, had a mean age of 56 years, and were 48% Hispanic, 35% African American, 13% Caucasian, and 4% other race/ethnicies. Standardized mean difference between groups showed female sex (.377), arrival by emergency medical services transport (.678), systolic blood pressure (.458), atrial fibrillation / flutter (.369), and NIHSS score of 10 – 14 (.426) were highly unbalanced.

Table 2 displays the results of the linear regression, showing the influence and estimated effect of patient demographic and clinical factors on continuous door-to-needle time. Female sex was associated with a total door-to-needle time increase of 14 minutes (95% CI, 3.412 - 27.111) and every per-minute increase in onset-to-arrival time was associated with a mean door-to-needle time increase of .12 minutes (95% CI, 0.00 - .246). Blood pressure, NIHSS score, age, race, emergency medical services transport, and patient comorbidities (e.g. atrial fibrillation / flutter) did not have a significant effect on door-to-needle time in the analysis.

Table 3 shows the comparison of the time taken to complete each of the 11 tPA administration benchmarks with standard target times for each benchmark. Median benchmark times did not show evidence of delay in any benchmark in comparison with target benchmark times.

4 | DISCUSSION

We found a relationship between increased door-to-needle times and female sex, based on the results of Table 1 and Table 2. Our finding of a mean total increase of 14 minutes highlights several challenges. First, for female patients, a urine pregnancy test may be performed prior to therapy because of the risk of uterine bleeding with tPA administration. Historically, tPA usage in pregnancy has been considered a relative contraindication. Earlier reviews of the small number of published case reports on this topic found varied results, from fetal demise to safe maternal and fetal outcomes (16-19). More recent findings and current guidelines leave tPA administration in pregnant patients with acute ischemic stroke up to physician discretion when the benefits of treating moderate or severe stroke outweigh the risks of uterine bleeding (2, 20-22). We suggest the need of further studies on the rates of physician usage of tPA in pregnant patients with acute ischemic stroke, and on the effect of across-the-board urine pregnancy testing on door-to-needle times. In the ED, the mean time to results of a urine pregnancy test available is 7.6 minutes if done at point-of-care and 32.6 minutes if sent to a laboratory (23), which may explain the difference seen in our patient population.

Past studies have shown that there are sex differences in the clinical presentation of acute ischemic stroke, with female patients presenting with fewer classic symptoms such as hemiparesis (24-26). Our findings are in line with studies that show female patients have greater delays in acute ischemic stroke treatment. Additionally, emergency medical services transport was utilized by slightly more male than female patients (55% vs 45%) which may have contributed to the door-to-needle time discrepancy. The causes for these delays are unknown, but it is possible that atypical acute ischemic stroke presentations may be contributing to these delays, as well as the possibility of physician or other provider bias.

While Table 1 shows that other variables, such as systolic blood pressure and atrial fibrillation / flutter, were also imbalanced, linear regression in Table 2 did not find a significant association with delayed door-to-needle time among these variables. Therefore, we view the statistically significant 14 minute mean door-to-needle increase for female sex as the most important finding from these analyses. Additionally, based on the results in Table 2, we technically found a statistically significant relationship between increased door-to-needle times and onset-to-arrival times. Time from symptom onset to hospital arrival is an established factor in eligibility for ischemic stroke interventions, such as tPA administration. The p value in our study of .049, however, is borderline at best, and the confidence interval contains zero. We therefore interpret this result conservatively and treat it as a non-significant result. In other literature, a study of 413,147 ischemic stroke patients from 2003 – 2006 found that over 25% of patients with ischemic stroke

Patient Factors*	Door to Needle Time Group (%)		Standardized Mean Diff
	0-60 min (n=38)	61-270 min (n=33)	(absolute value)
Age (years), mean (SD)	56.92 (13.93)	55.70 (10.04)	0.101
Female, sex	42.1% (n=16)	60.6% (n=20)	0.377
Race			
Caucasian	(S†)	15.15% (n=5)	0.139
African American	34.2% (n=13)	36.36% (n=12)	0.045
Hispanic	50% (n=19)	45.45% (n=15)	0.091
Asian	S†	S†	0.024
Other	S†	0.00% (n=0)	0.233
NIHSS, median (IQR)	10 (7-15)	9 (6-16)	
0-9	42.11% (n=16)	57.58% (n=19)	0.313
10-14	28.95% (n=11)	12.12% (n=14)	0.426
>14	28.95% (n=11)	30.30% (n=10)	0.030
Systolic BP, mm Hg mean (SD)	153.18 (28.31)	168.48 (37.89)	0.458
Diastolic BP, mm Hg mean (SD)	89.58 (14.77)	93.88 (21.22)	0.235
Onset to arrival time, mean (SD)	75.95 (46.11)	73.12 (61.39)	0.052
Arrival by EMS	68.4% (n=26)	36.36% (n=12)	0.678
Comorbidities			
AFib/flutter	S†	S†	0.369
Hypertension	65.79 (n=25)	78.79% (n=26)	0.294
CAD	13.16% (n=5)	15.15% (n=5)	0.057
Carotid stenosis	(S†)	0.0% (n=0)	0.232
Diabetes mellitus	34.21% (n=13)	36.36% (n=12)	0.045
Dyslipidemia	28.95% (n=11)	24.24% (n=8)	0.107
Heart failure	S†	S†	0.245
Migraine	S†	0.0% (n=0)	0.233
Obesity/overweight	S†	0.0% (n=0)	0.233
Previous AIS	35.58% (n=12)	36.36% (n=12)	0.101
Sickle cell	0.0% (n=0)	S†	0.250
Smoking	23.68% (n=9)	30.3% (n=10)	0.150

*Abbreviations: NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; EMS, emergency medical services; BP, blood pressure; AFib, Atrial fibrillation; CAD, coronary artery disease; AIS, acute ischemic stroke. S† number suppressed to preserve patient confidentiality.

TABLE 1 Comparison of Characteristics of Patients in Timely and Delayed Door-to-Needle Time.

do arrive within the window for tPA administration (27). More recently, another study from the early containment phase of the coronavirus-19 pandemic did not find any evidence of delayed door-to-needle times (28), despite differences in onset-to-arrival times between pre-covid and covid groups.

We also did not find evidence of a delay in any specific benchmark, based on crude comparison of median benchmark times with target times in Table 3. While the AHA / ASA Target: Stroke initiative has provided target

Patient Factors*	Minutes Faster, min (95% CI)	*p*
Age, per year decrease	-0.4 (-0.94 to 0.14)	0.15
Sex		
Male	14.0 (3.4 to 27.1)	0.037
Female	0 [Reference]	
Arrival Mode		
EMS	6.5 (-11.5 to 24.5)	0.48
Non-EMS	0 [Reference]	
NIHSS		
0-9	0 [Reference]	
10-14	15.4 (-1.9 to 32.6)	0.08
>14	12.3 (-3.1 to 27.7)	0.12
Systolic BP (per 1 mmHg increase)	- 0.0 (-0.2 to 0.2)	0.92
Diastolic BP (per 1 mmHg increase)	0.0 (-0.3 to 0.4)	0.80
OTA time per min decrease	0.1 (0.0 to 0.2)	0.049
Comorbidities		
AFib/flutter	12.2 (-7.1 to 31.4)	0.21
No AFib/flutter	0 [Reference]	
Hypertension	0.0 (-15.1 to 15.1)	0.99
No hypertension	0 [Reference]	
CAD	7.2 (-12.3 to 26.6)	0.47
No CAD	0 [Reference]	
Carotid stenosis	19.2 (-38.1 to 76.6)	0.51
No carotid stenosis	0 [Reference]	
Diabetes mellitus	- 7.2 (-21.3 to 6.8)	0.31
No diabetes	0 [Reference]	
Dyslipidemia	-0.9 (-16.2 to 14.4)	0.91
No dyslipidemia	0 [Reference]	
Heart failure	- 11.2 (-35.4 to 13.1)	0.36
No heart failure	0 [Reference]	
Migraine	30.4(-26.7 to 87.4)	0.29
No migraine	0 [Reference]	
Obesity/overweight	15.2 (-42.3 to 72.6)	0.60
No obesity/overweight	0 [Reference]	
Previous AIS	1.6 (-12.7 to 15.9)	0.82
No previous AIS	0 [Reference]	
Sickle cell	-30.5 (-87.5 to 26.6)	0.29
No sickle cell	0 [Reference]	
Smoking	- 2.7 (-18.0 to 12.6)	0.72
No smoking	0 [Reference]	

*Abbreviations: DOOR-TO-NEEDLE, door-to-needle; EMS, emergency medical services; NIHSS, National Institutes of Health Stroke Scale; OTA, onset-to-arrival; BP, blood pressure; AFib, Atrial fibrillation; CAD, coronary artery disease; AIS, acute ischemic stroke.

TABLE 2 Linear Regression Analysis of Patient Factor Effect on Door-to-Needle Time

Benchmark*	Time to Complete Benchmark (Min)		Target Time (min)
	Median	Quartiles [Q1, Q3]	
Triage Done	0.0	[0.0, 3.3]	≤ 1
Stroke Alert Paged	2.0	[1.0, 6.3]	≤ 5
Patient to CC Room	3.0	[1.0, 9.3]	≤ 5
EM Faculty at Bedside	4.0	[2.0, 8.0]	≤ 5
Neurologist at Bedside	5.0	[2.0, 11.0]	≤ 15
Blood Carried to Lab	8.5	[5.0, 15.0]	≤ 15
Head CT Performed	15.0	[10.0, 21.3]	≤ 25
Verbal Results of Head CT	18.5	[11.0, 24.3]	≤ 45
Head CT Results in Epic	29.5	[23.0, 40.3]	≤ 45
CBC, PT/INR/PTT in EMR	37.5	[28.4, 59.6]	≤ 45
tPA Ordered	38.7	[30.4, 55.0]	≤ 50

*Abbreviations: tPA, tissue plasminogen activator; DOOR-TO-NEEDLE, door-to-needle; CC, critical care; EM, emergency medicine; CT, computed tomography; EMR, electronic medical record; CBC, complete blood count; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time.

TABLE 3 Comparison of individual tPA administration benchmarks times with target time for each benchmark

times for each benchmark (6), further research is needed to identify key "bottlenecks" causing delays in tPA workflow. Such findings would have important clinical relevance because they would demonstrate where specific delays are occurring in the tPA administration workflow, providing an opportunity for targeted optimization to decrease door-to-needle time.

Many quality improvement programs have been effective in reducing door-to-needle times. A notable example is the Helsinki stroke thrombolysis model (29), which achieved a median door-to-needle time of 20 min in Finland. This model has been implemented in other settings such as Melbourne, Australia, where it achieved a 25 minute reduction in overall median door-to-needle time (from 61 minutes to 46 minutes) (30), and Christchurch, New Zealand, where overall median door-to-needle was reduced from 87 minutes to 40 minutes (31). The Helsinki protocol includes 1) ambulance pre-notification mobilizing the stroke team to receive the patient; 2) patients moved from triage to CT while still on the ambulance stretcher; and 3) delivery of tPA in CT immediately following imaging. The success of this model when transferred from Europe to other continents underscores the potential for similar results to be attainable in other settings. Therefore, future research should also consider whether features of this model are transferrable to settings such as the US and Canada and evaluate their impact, if any, on door-to-needle times.

Our study is limited by the small sample size, use of a single ED location, and the retrospective design. Nonetheless, our results are clear and consistent with prior studies. While the sample size of 71 ischemic stroke patients is too small to act as a nationally generalizable sample, the number does reflect the full population of ischemic stroke patients presenting to Ben Taub County Hospital ED over a three-year period and was large enough to permit valid statistical analysis. Second, with respect to the use of a single ED, it is true that differences in hospital EMR systems, laboratory resources, staffing ratios, and general level of expertise (e.g. whether the hospital had an in-house stroke unit) may significantly impact patient care. However, by focusing on a single ED, we reduce variations that may lead to improper analysis, as different EDs may use different benchmarks for tPA administration.

The limitations introduced by using a retrospective

study design merit additional discussion. Data recorded on pre-hospital notification was incomplete and thus removed from our analysis. Older and more recent studies however have found an association between pre-hospital notification and arrival via emergency medical services with decreased door-to-needle times (9, 11, 32-37). Provider bias may also be a factor in these results, as patients coming to the ED by ambulance are often treated with a greater sense of urgency which may contribute to faster door-to-needle times (38). Third, although it is possible that female patients presented with less classic signs and symptoms which caused a more delayed door-to-needle time, the scope of our chart review was limited to comparisons of overall National Institutes of Health Stroke Scale score and not individual variability in signs and symptoms.

Additionally, the 2013 AHA / ASA guidelines were updated in 2018 and 2019 (2, 39) which may have modified current provider practices. While most guidelines were either unchanged, reworded for clarity, or had their level of evidence reclassified, two new recommendations for ischemic stroke are worth note. First, guideline 1.5.3 proposes it may be reasonable to establish a secondary goal of door-to-needle times within 45 minutes in $\geq$ 50% of patients with AIS who were treated with IV alteplase. This is based on a study of 16,901 patients with ischemic stroke (treated with IV alteplase 4.5 hours of symptom onset) where 30.4% were treated 45 minutes after hospital arrival (40). Second, guideline 1.5.5 recommends that "multicomponent quality improvement initiatives, which include ED education and multidisciplinary teams with access to neurological expertise, are recommended to safely increase IV thrombolytic treatment." This recommendation is based on the US cluster-randomized INSTINCT trial (Increasing Stroke Treatment Through Interventional Change Tactics), which demonstrated increased rates of alteplase use among the intervention group (41). While these recommendations have the potential to alter current and future practices with respect to the door-to-needle time workflow, they do not influence our findings for the years 2010 – 2013. Therefore, we recommend that comparison of our findings to more recent data would be a valuable direction for future research.

As a final note, stroke severity is an important confounder of unadjusted door-to-needle time analysis as increased severity can increase the likelihood of earlier presentation and worse outcome (42). Our study, however, focused specifically on potential delays in the workflow of tPA administration, not outcome differences. Better adjustment for confounders and a more thorough study design would be necessary to evaluate whether there is such an association. Nevertheless, there is already strong evidence that delayed door-to-needle times leads to poorer outcomes (4, 5, 13, 42, 43).

In conclusion, we found that female sex is associated with delayed door-to-needle time but did not find evidence of delays in any specific tPA administration benchmark. Further investigation into these areas may allow for optimization of workflow leading to decreased door-to-needle times and improved patient outcomes.

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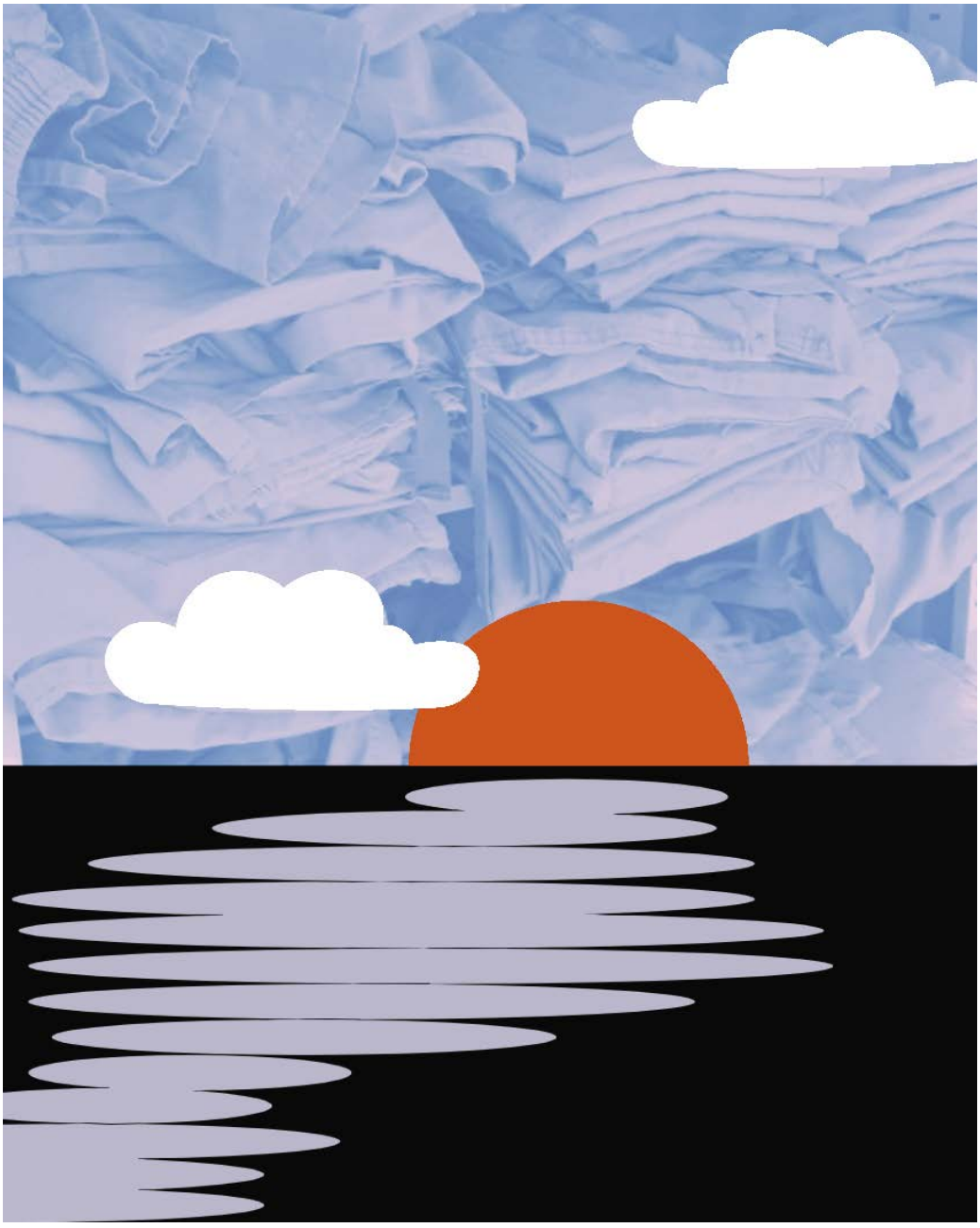
SYSTEMATIC REVIEW



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SYSTEMATIC REVIEW
McGill Journal of Medicine

The Effect of Perceived Weight Gain on Hormonal Contraception Choice for Women: A Review

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ABSTRACT

Background: Hormonal contraception plays a pivotal role in protecting against unintended pregnancies and has been developed to provide options that best fit women's lifestyles. However, negative perceptions can alter women's attitudes and prohibit the use of hormonal contraception. This review aimed to collect information surrounding perceptions of side effects due to hormonal contraception, specifically, perceptions of weight gain, and their influence on women's contraceptive choice.

Methods: 703 articles were found through searching three electronic databases: EBSCO, PubMed, and Web of Science; in addition to Google Scholar. Articles were included if published between 2009-2020, could be translated to English, included any form of hormonal contraception, and reported perceived weight gain. A total of 39 articles met the inclusion criteria and were included in the review.

Results: Within those articles, there were six overarching themes: (1) negative perception of weight gain, (2) fear of weight gain, (3) contraception decision based on obesity concerns, (4) avoidance and discontinuation of the hormonal contraception due to concerns of weight gain, (5) limited contraceptive knowledge, and (6) lack of counseling. Women's perceptions and attitudes of contraceptive methods were shaped by both belief and perceptions, i.e., women who believed weight gain a side effect of HC and/or had negative perceptions of contraceptive related weight gain influenced their overall perceptions and attitude of a contraceptive method.

Conclusion: Negative perceptions are derived from experience, misconception, and lack of knowledge; this leads to fear, avoidance, or discontinuation. Understanding women's perceived weight gain and perception towards contraceptives can help assess its effect on women's choice of contraception. This information can aid health care professionals in educating and discussing methods that would best fit women and improve hormonal contraception adherence.

KEYWORDS

Hormonal contraception, Weight, Perception, Women

1 | BACKGROUND

Family planning methods, specifically hormonal contraception (HC), have become increasingly popular globally among individuals of reproductive age. Commonly used HC methods include oral contraceptive pills, vaginal rings, injectable contraceptives, transdermal contraceptive patches, and long-acting reversible contraceptives (LARCs): intrauterine devices (IUDs) and contraceptive implants. Women seek HC for their effects on pregnancy prevention, menstrual consistency, and acne control. Method effectiveness and longevity can vary, allowing users to choose the method that best fits their lifestyle.

While the effectiveness of HC methods can be appealing, their side effects can deter use and adherence. With more women reporting weight gain as a side effect, studies have tried to understand the role of HC methods on weight gain. Gallo and Lopez conducted a systematic review that found no evidence that pills or patches caused any weight change. (1) While there is a lack of scientific consensus on whether pills, patches, rings, and IUDs induce weight change, injectable HC has been shown to cause weight gain (mean weight gain of >2kg). (2) Women are more likely to use oral contraceptives (88%) than injectable contraceptives (23%). Therefore, women who use oral contraceptives as their HC method should not experience the side effect of weight gain. (3)

Since the 1960s, the percentage of US women who are overweight, obese, or severely obese has consistently been higher than that of males. (4) Furthermore, the proportion of women transitioning from normal to overweight and overweight to obese has increased annually since the 1960s. (4) As women perceive themselves at risk for obesity, fear of weight gain becomes more prominent. Women with obesity concerns may view weight gain from HC as detrimental. This can influence their perception (consciousness) and attitude (feeling/emotion), thus creating a barrier to contraceptive adherence regardless of BMI.

Many articles have studied actual weight gain caused by hormonal contraceptives, but few attended to the perceptions of weight change and how they affect the use of contraception. This literature review strived to examine the relationship between perceived weight gain from hormonal contraceptives and contraceptive decisions among women of reproductive age.

2 | METHODS

2.1 | Search Strategy

Data were retrieved from EBSCO, Google Scholar, PubMed, and Web of Science between January and February 2020. The initial search included studies related to hormonal contraception and perceived weight change in women. The final keywords included: discontinuation; weight perception; body weight; birth control; weight gain; hormonal contracept*; perceived weight; qualitative; side effects; body image; knowledge, attitudes, and behaviors. An emphasis was placed on searching perceived weight gain and qualitative data to find self-reported data rather than actual measurements of weight gain while using HC methods. The final search terms are outlined in Table 1.

2.2 | Selection Process

Covidence online software was used to manage the review process, as displayed in Figure 1 (Covidence systematic review software). The initial search resulted in 703 articles. After removing duplicates, 379 articles remained. Those 379 articles were then screened by title and abstracts by a team of five researchers. Two votes were required to include/exclude the articles, and the primary investigator resolved all conflicts. Through the abstract screening process, 119 articles proceeded to full-text screening, 80 of which were removed. A total of 39 articles were thus included in the review.

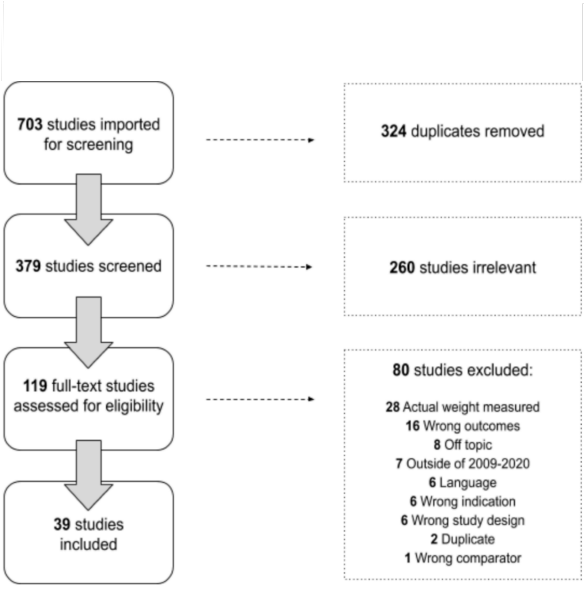

FIGURE 1 PRISMA Table of Screen Process.

3 | RESULTS

3.1 | Study Characteristics

Most articles discussed negative perceptions of weight gain from hormonal contraceptives (69%, N=39). Sixteen (41%, N=39) articles examined women of all reproductive ages, while another sixteen studied married women (39.0%, N=39), and seven focused on adolescents or college-aged women (17.0%, N=39). Studies varied in contraceptive method focus: multiple family planning methods including condoms, vasectomy, and hormonal contraceptives, hormonal contraceptives only, oral contraceptives, IUDs, injections, LARCs, ring, implants. (2, 3, 5, 8, 13) Thirty-six studies focused on perceived adverse effects regarding hormonal contraceptive side effects, while three studies examined the perception of both positive and negative effects. Weight gain as a side effect was identified in twenty-seven studies. The detailed characteristics of the studies are summarized in Table 3. In general, articles displayed six overarching themes: (1) negative perception of weight gain, (2) fear of weight gain, (3) contraception decision based on obesity concerns, (4) avoidance and discontinuation of the contraceptive method due to concerns of weight gain, (5) limited contraceptive knowledge, and (6) lack of counseling. The detailed characteristics of the studies and themes are summarized in Table 2.

3.2 | Negative Perceptions of Weight Gain

Negative perceptions, defined as knowledge, attitude, or beliefs regarding HC, were reported in thirty-four studies. Knowing someone with a negative experience was also reported to significantly influence acceptance of a given HC method. (5-11) Studies reported that women with negative perceptions were less likely to adhere, thereby reducing a method's efficacy. (12) Many women stated weight gain was an undesirable side effect of HC methods. (13-22) Women preferred to avoid factors that changed their bodies and viewed them negatively. (23, 24) Among those who used oral contraceptives, 34% (N=615) noted that no effect on weight was the most important feature of their oral contraceptive choice, and 46% (N=615) of women stated that weight gain was the side effect they were most concerned about. (25)

Twelve articles discussed the fear of weight gain. Women feared weight gain as a side effect, perceiving it as undesirable and harmful. (20, 23, 26) Fear of gaining weight was noted as a top reason for women's non-use or discontinuation of HC. (7, 9, 19, 21, 27-29) For example, among Northern Nigerian women, the most significant contributor (77.2%, N=334) in the non-use of HC methods was the fear of side effects; of which 83.8% (N=334) perceived weight gain as a side effect. (28)

Four studies examined how women's negative perception of weight gain from HC methods was related to obesity concerns. Obesity was cited as a feared side effect for some women, which contributed to their non-use of injectable methods. (7) In general, women who perceived themselves as overweight or obese were conscious of how their contraceptive decision affected their body weight. (30) Women with these perceptions were more likely to choose LARCs over injectable methods or avoid either method altogether. (30) Furthermore, while using LARCs, overweight or obese women reported more weight gain perception than women with

normal weight. (31, 32)

Twenty-two articles discussed the avoidance of HC due to weight gain concerns. Many women cited weight gain as their main reason for avoidance. (7, 8, 10, 21, 27, 28, 30, 33-36) Women wanted to avoid methods they believed caused weight gain, even if not scientifically proven.

Discontinuation was the most common result of weight gain-related perceptions. After six months, women who reported weight changes were less likely to continue their oral contraceptive methods. (16) This was especially true if women perceived drastic weight changes. (17) Contraceptive discontinuation was also influenced by combined side effects such as weight gain and anxiety or headache. (11, 18, 31, 37-41)

3.3 | Misperceptions or Limited Contraceptive Knowledge

Seventeen studies concluded that women received incomplete counseling regarding the side effects of HC. Lack of counseling influenced decision making, weighted by fear of side effects, such as potential weight gain. In a South African study, women reported that their providers merely gave suggestions on a contraceptive method rather than providing comprehensive information to make their own decisions. (10) A study on university women in Colombia concluded that 41.4% (N=353) of women thought contraceptive counseling was lacking. (18) Women in rural Mexico demonstrated awareness of a HC method but insufficient knowledge due to ineffective counseling. (26) In the US, the underuse of LARCs is related to a lack of awareness or knowledge from potential users and clinicians. (31)

Women relied on personal relationships such as friends and family, who often provided misinformation, when contraceptive counseling fell short. (21) Ibrahim and Rabiu also noted that women cited nurses, midwives or the media as their primary sources of information, indicating that effective counseling does not stem only from physician providers. Moreover, inadequate counseling of side effects is a significant predictor of discontinuation. (28, 38) Accordingly, women who were better informed about the implants' expected side effects were more likely to continue with the method. (39) Thus, contraceptive counseling can be imperative to awareness of options and knowledge of HC methods and associated side effects; it can also influence satisfaction with the chosen method and trust in providers. (9, 12, 22, 24, 29, 40, 42)

Fifteen articles demonstrated that a lack of contraceptive knowledge was the reason for perceiving or predicting weight change when using a HC. Contraceptive knowledge includes information about proper use, mechanism, efficacy, advantages, and side effects. Lack of knowledge resulted in overestimation of the risks and underestimation of the benefits associated with HC, and correlated with negative experiences in general. (37,43)

Women's educational level, self-reported in surveys, interviews, and focus groups, was established as the reason why some women were not knowledgeable of HC methods. (6, 8, 14) However, da Silva-Filho found that higher education does not correlate with better contraceptive knowledge. Women with higher education (more than 12 years) overestimated risk, similarly to women without higher education, and emphasized anecdotal information instead of healthcare providers' recommendation. (8) A study in Turkey found that misconception of combined oral contraceptive pills (COCPs) was prevalent, 45.2% (N=418) believed that COCPs cause weight gain, and 27.5% were unsure if COCPs caused significant weight gain. (29)

4 | DISCUSSION

The findings of this review indicate that negative perceptions of weight gain from HC may influence women's contraception decisions. As Lopez et al. established, most HC methods lack scientific consensus to determine their causal role in actual weight gain. This is consistent with a study done by Beksinska, where clients commonly perceived weight gain from HC methods even when actual weight gain has not been associated with the method in scientific studies. (44) This review reported that while there is not a consensus to validate

the causation of weight gain from HC methods, women consistently discontinue their hormonal methods due to perceived weight gain. (44) Beksinska and Smit also noted that healthcare providers themselves might harbor negative perceptions of these methods, affecting prospective users. (44)

Women reported perceived weight gain as a negative side effect of most HC methods, although limited evidence exists to prove such a theory. (1) Informational websites, packaging, and organizations such as the American Family Physician, often list weight gain as a side effect and include it in counseling users. (45) As the data is inconclusive regarding weight gain as a side effect, there is misinformation and confusion surrounding this. Information provided on contraception labels and during contraceptive counseling can negatively shape women's perceptions even if the possibility of gaining weight due to the method is low.

The studies found that women mainly learned about side effects of contraception from first and second-hand experiences rather than health professionals. Many women did not receive counseling or were given false information regarding the HC method and weight change (I.e. this method does not cause weight gain). Weight gain was often cited as the top side effect of HC, and such negative experiences often outweighed the benefits of pregnancy prevention. Misinformation plays a role in a woman's decision to discontinue HC. Although we recognize that many women may not have conversations with their providers regarding misconceptions, it may be worth investing in a patient centered reproductive justice framework to dispel some of these myths. Paying special attention to people of color and other marginalized communities who may have experienced historical and ongoing reproductive mistreatment could make a significant difference in these perceptions among women.

Citing perceived weight gain as a primary reason for discontinuation indicates that negative perception or misinformation affects women's satisfaction. Whether women are gaining weight or not, the perception of gaining weight is a significant indicator of utilization. A woman's perception of her weight while using HC methods is equally as important as the number on the scale regarding satisfaction and continuation of a HC method. (32) Women with negative experiences with HC methods were less likely to use contraceptives again. (13, 23) Some women frequently changed HC methods because they believed they were gaining weight.

Women with obesity concerns may prioritize weight maintenance over effective family planning methods. Women who perceived themselves as obese were more inclined to avoid or choose certain hormonal contraceptives. These decisions stemmed from the perception that some methods, such as injectable HC, caused more weight gain over others (for example, LARC), or that no method prevents weight gain. Thus, even if women were not obese, these perceptions are enough to influence their contraceptive decision. Women who are concerned about obesity are predisposed to perceiving weight gain for any reason. This may bias women's perception that actual weight gain occurred, leading to discontinuation of HC methods. (31, 32) Also, those concerned with their weight may be more sensitive to any perceived changes. Healthcare providers need to be considerate of weight or obesity concerns when discussing hormonal methods.

Mismatched HC method information was another theme that arose from the literature, causing women to believe myths about HC methods and weight gain. (44) There are various reasons why women do not have proper knowledge of HCs. Women report that information provided during HC counseling often does not align with the information they want to know, further contributing to discontinuation or utilization. Women's educational level may play a part as limited education could be correlated to living in poor or medically underserved regions. Women in these areas may be more susceptible to misconceptions. Nonetheless, women with higher education may also harbor misconceptions based on anecdotal information from peers. (8) The prevalence of weight gain misperceptions explains why a woman might think she is gaining weight while using a HC method.

While women were informed about HCs efficacy for family planning, misinformation on its side effects

served as a prominent barrier to HC usage. Healthcare providers' awareness of negative perceptions may be useful in approaching conversations about perceived side effects. Providers could eliminate misconceptions about the risk of weight gain through counseling to create more positive experiences for women using a HC method. Improved counseling was shown to reduce the rate of unwanted pregnancy in populations that included women from racially and socioeconomically diverse backgrounds. (42) By clarifying the misbelief surrounding weight gain, women worldwide may be less likely to discontinue the use of a HC method and practice healthy family planning methods.

This literature review found six overarching themes relating to negative perceptions of hormonal contraceptives and weight gain, which could instill non-acceptance towards the method. Understanding women's perception of hormonal contraceptives can facilitate appropriate conversations based on women's concerns. As hormonal contraception becomes more accessible to women, the next step includes increasing continuation rates and satisfaction.

5 | LIMITATIONS

This review examined open-access, peer-reviewed studies observing the relationship between hormonal contraception and perceived weight change. Limitations may exist because the 39 reviewed articles did not cover all available hormonal contraceptive methods in-depth since a frequent focus of available articles was on oral contraceptives. Actual reports of weight gain were excluded, even if self-measured, due to the chance that perceptions could be altered. The exclusion of actual weight is a limitation as it significantly reduced the articles available for review and may present a perspective missing in our data. Additionally, some articles were excluded if they could not be translated into English, and sample sizes varied among the studies making the conclusions difficult to generalize across groups.

6 | CONCLUSIONS

Women need improved hormonal contraception counseling from a healthcare professional when deciding on a HC method that best fits their needs. Understanding women's perception of hormonal contraceptives can facilitate appropriate conversations to personalize contraceptive usage based on individual concerns. Since hormonal contraception plays a relevant role in women's sexual health, next steps include improving HC continuation rates and increasing satisfaction. This study indicates that while there isn't scientific consensus on weight gain causation from contraceptive methods women are in need of hormonal contraception counseling that dispels existing misinformation regarding the risk of weight gain with HC use. Women often perceive that HC counseling does not address their concerns about side effects, including weight gain. The next step to address these issues may be to develop patient centered HC counseling resources for providers to improve women's acceptance and satisfaction using HC.

CONFLICTS OF INTEREST

None declared

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TABLE 1 Search Terms

	Data Bases	Search Terms	Exclusion Terms
Web of Science	– BIOSIS Previews – Web of Science Core Collection – MEDLINE	– Contracep* "side effect" AND weight AND qualitative – "Body weight" OR "body perce*" AND contracep* – Weight percept* OR perce* weight AND contracep* – Contracep* AND weight AND qualitative – Knowledge OR attitudes OR beliefs AND contracep* AND weight – "Body image" OR "body weight" AND contracep* – "Weight percep*" OR "weight gain" OR "body image" OR "percei* weight" AND contracep*	–emergency OR –abort* OR –male OR –fert OR –"unintended pregnancy"
EBSCO	– CINHAL plus with full text – Academic Search Premier	– Contracep* "side effect" AND weight AND qualitative – "Body weight" OR "body perce*" AND contracep* – Weight percept* OR perce* weight AND contracep* – Contracep* AND weight AND qualitative – Knowledge OR attitudes OR beliefs AND contracep* AND weight – "Body image" OR "body weight" AND contracep* – "Weight percep*" OR "weight gain" OR "body image" OR "percei* weight" AND contracep*	–emergency OR –abort* OR –male OR –fert OR –"unintended pregnancy"
Google Scholar		– Contracep* AND "side effect" AND weight AND qualitative – Contracep* AND "body weight" OR "body perce*" – "Weight percept*" OR "perce* weight" AND contracep* – "Birth control" AND weight AND qualitative – Contracep* AND weight AND knowledge OR attitudes OR belief – "Body image" OR "body weight" AND contracep* – "Weight percep*" OR "weight gain" OR "body image" OR "percei* weight" AND contracep*	–emergency OR –abort* OR –male OR –fert OR –"unintended pregnancy"
PubMed		– Contracep* "side effect" AND weight AND qualitative – "Body weight" OR "body perce*" AND contracep* – Weight percept* OR perce* weight AND contracep* – Contracep* AND weight AND qualitative – Knowledge OR attitudes OR beliefs AND contracep* AND weight – "Body image" OR "body weight" AND contracep* – "Weight percep*" OR "weight gain" OR "body image" OR "percei* weight" AND contracep*	–emergency OR –abort* OR –male OR –fert OR –"unintended pregnancy"

TABLE 2 Article characteristics

	Location	Contraceptive	Participant Characteristics	Findings
Agasti et al., 2017	Orissa, India	Family planning methods (condom, OCP, IUD, vasectomy, etc.)	n=36 age=N/A Setting: tribal health center	Questionnaires administered to healthcare workers found that they may have pre-existing biases against weight gain from contraceptives and could be influencing their clients' biases during consultations.
Al-Mass et al., 2018	Riyadh, Saudi Arabia	Oral contraceptive pill	n=462 age=14-50 Setting: public shopping mall	More married women perceived weight gain than unmarried women. Regular OC users perceived more weight gain than irregular OC users. The article also noticed the belief that OCs will cause weight gain.
Altaf et al., 2017	Chicago, US	Birth control	n=23 (focus group), 1442 (survey) age=N/A Setting: focus group discussions	Survey was administered to college women to which 23/1442 were engaging in sexual behaviors without contraception due to fear of weight gain from contraceptives. Women with low body shame scores showed that negative body image correlates to fear of weight gain from contraceptive.
Bajwa et al., 2011	Punjab, India	Condom, Oral contraceptive pill, IUD	n=1123 age=15-49 setting: Rural Health Training Center	A survey done in India determined that pills were perceived to cause weight gain as shown by the 38% who were not using OCP due to fear of weight gain.
Bardaweel et al., 2015	Amman, Jordan	Oral contraceptive pill	n=1571 age=18-50 Setting: distributed questionnaire	Those with experiences of weight gain as a side effect were more likely to possess negative attitudes about OC's efficacy. Occurrence of side effects was identified as the major reason for discontinuation. Positive attitude towards OC efficacy and safety was associated with their pattern of use.
Bardaweel et al., 2018	Jordan	Oral contraceptive pill	n=425 age=18-50 Setting: refugee	When asked about knowledge, attitude, and experience with hormonal contraceptives, refugee women showed that 60% feared the side effects and 30.6% of those discontinued was due to weight gain. Lack of knowledge of the method correlated with a negative experience with, and negative attitude towards the hormonal contraceptive.
Belete et al., 2018	Humera town, Ethiopia	Modern contraceptive (condom, OCP, injectable, IUCD, implant)	n=321 age=15-29 Setting: distributed questionnaire	This study on married women in Humera Town, Ethiopia revealed that 31.1% of those who experienced side effects discontinued, 34.7% of which was due to weight gain. Majority of the discontinuous responded that the reason for discontinuation was desire to get pregnant, while a major reason for non-use was due to fear of side effects.

Bhuva et al., 2017	Pennsylvania, US	LARC, non-LARC	n=987 age=18-40 Setting: distributed survey	Women who perceived that they were overweight were more likely to choose LARC (over other hormonal methods) than women who perceived normal weight (adjusted ratio showed that there is no association between weight and choice, however). Perception of overweight in women was linked to decreased likelihood of DMPA usage due to weight concern.
Chernick et al., 2015	New York,US	Injectable (depo) IUD, intravaginal ring, implant, patch, pills	n=14 age=14-19 Setting: emergency department	Interviews showed that barriers of contraception use regarding weight included: Concerns about getting “fat”, Negative attitude because of past experience, Previous contraceptive method changed their body, and causes “bloating”. The subjects engaged in non-use or inconsistent use of contraceptives while being sexually active. Those with a previous negative experience showed mistrust and were unwilling to try contraception again.
Chipeta et al., 2010	Mangochi district, Malawi	Family planning (pills, condoms, loop, injections)	n=1115 age=15-65 Setting: focus groups in south Malawi	Depo-provera was the most common modern method used, and included in the reported reasons for non-use of depo included fear of weight gain and obesity. Oral contraceptives were also common. Negative attitudes, myths, and beliefs were present among females in regards to modern contraceptives due to its possible damage to organs.
Clare et al., 2016	New York, US	Depo, LARC (copper IUD, implant rods)	n=** age=13-21 setting: Adolescent Clinic of Metropolitan Hospital Center	Survey taken at the Adolescent Clinic of Metropolitan Hospital Center revealed weight gain as a common concern for young adults using depo and LARC. Early adults were also concerned about privacy from parents about their contraceptive habits. These concerns can serve as a major barrier to contraceptive use.
Coombe et al., 2016	Australia, USA, New Zealand, Japan, Canada, Western Europe	LARC	n=30 age=18-23 Setting: systematic review on developed countries	The systematic review noticed the prevalence of weight gain as a negative quality. Gubrium 2011 described the impact of women’s fear of side effects and Glasier et al 2008 reported that fear of side effects as well as hearing of other’s experiences can impact. There was also a general trend of increased familiarity of a method increasing attitude towards the method.

Da Silva et al., 2016	Brazil, Argentina, Columbia, Mexico	IUD	n=1953 age=20-30 Setting: nursing and medical market research panel	Of those who attended the nursing and medical market research panel, the questionnaire examined that perceived weight gain was reported by 38.2% of LGS IUS users and 14.3% of copper IUD users. Those from higher education placed value on anecdotal information of healthcare providers. There was an overestimation of risk which prohibited use of the most effective method for them due to their misperceptions.
Dansereau et al., 2017	Chiapas, Mexico	Family planning methods (implants, pills, injectables, condoms)	n=292 age=not stated Setting: focus group discussion	In the study, most participants agreed on the importance of family planning, but many also knew of those who were opposed to it. Both men and women had concerns about short- and long-term side effects of hormonal methods such as pills and injections, one of which was weight gain. A woman expressed her fear towards pills and injectables could possibly kill her, and that she would rather conceive than die of these methods.
Dickerson et al., 2013	South Carolina, US	LARC (IUD, SDI)	n=132 age =18 Setting: Medical University of South Carolina (MUSC) family medicine resident and faculty clinics	A survey of satisfaction, continuation, side effects of LARC found that discontinuation due to weight gain was 20% for SDI and 18.2% for IUD. More overweight and obese women reported weight gain than women of normal body weight.
Duvan et al., 2010	Turkey	implant	n=61 age=22-41 setting: Obstetrics and Gynecology Department of Fatih University, Medical School,	The study found that the combination of weight gain and anxiety was the second most common reason for discontinuation of Implanon. Weight gain was reported by 10 patients (16%), weight gain and headache by two (3.2%), and weight gain and anxiety by two (1.6%).
Fait et al., 2018	Czech Republic, Poland, Romania, Russia, Slovakia	Oral contraceptive	n=615 age≥25 setting: face-to-face surveys performed by experiences individuals	A survey of women from countries in Central and Eastern Europe found that 61% of women established positive views of OC when it did not cause weight gain. High proportion of women perceiving weight gain and 65% of women admitted they are worried about weight gain. When asked about OC's most important feature, 34% responded OC's no effect on body weight.
Fruzzetti et al., 2016	Italy	Pills, vaginal ring	n=1809 age=14-42 Setting: Outpatient clinic of Santa Chiara Hospital	The survey of attendants at an outpatient clinic in Italy observed 4.8% of women who discontinued due to weight gain and majority of the participants who observed weight gain were unable to quantify their statement.

Ghule et al., 2015	Maharashtra, India	oral contraceptive pill	n=62 age=15-24 Setting: in-depth interviews and focus groups	This qualitative study noticed fear of side effects of oral contraceptive pills when the husband reported their female partner's fear of weight gain as a reason for her discontinuation.
Gomez & Freihart, 2017	US	IUD	n=730 age=18-24 setting: online survey	432/730 of the surveyed women were not interested in getting the IUD because of health related fears, which included weight gain. Fears and concerns were noticed in participants who responded that they did not want an IUD. 124 subjects who responded that they were uninterested in ever getting an IUD displayed negative perception of the device, often citing social influences who shared with them their own negative experiences.
Gómez-Sánchez & Pardo, 2010	Bogotá, Columbia	Combined oral contraceptives (Injection, oral contraceptive, IUD, implants)	n=12 age=18-45 setting: proctored discussion in focused groups	A group of participants in the discussions stated all hormonal contraceptives produce side effects that are "unpleasant" which include weight gain. Others have stated that injectables can induce weight gain and that no weight change is optimal in hormonal contraceptives. When there is a perceived weight change though, participants stated that it could create fear or rejection in women through altering their bodies.
Hall et al., 2016	Michigan, US	LARC (IUD, implant)	n=1982 age≥18 Setting: college campus	This study noticed that when women were asked whether they were worried about the side effect of IUDs, 27.6% identified it as a barrier and 1.9% as a main reason for non-use. When asked the same question about implants, 24.9% identified it as a barrier and 2.6% as a main reason for non-use. The sample showed low understanding of the actuality of LARC's side effect of weight gain. The study generally noticed that misperception and negative perception can derive from lack of knowledge.

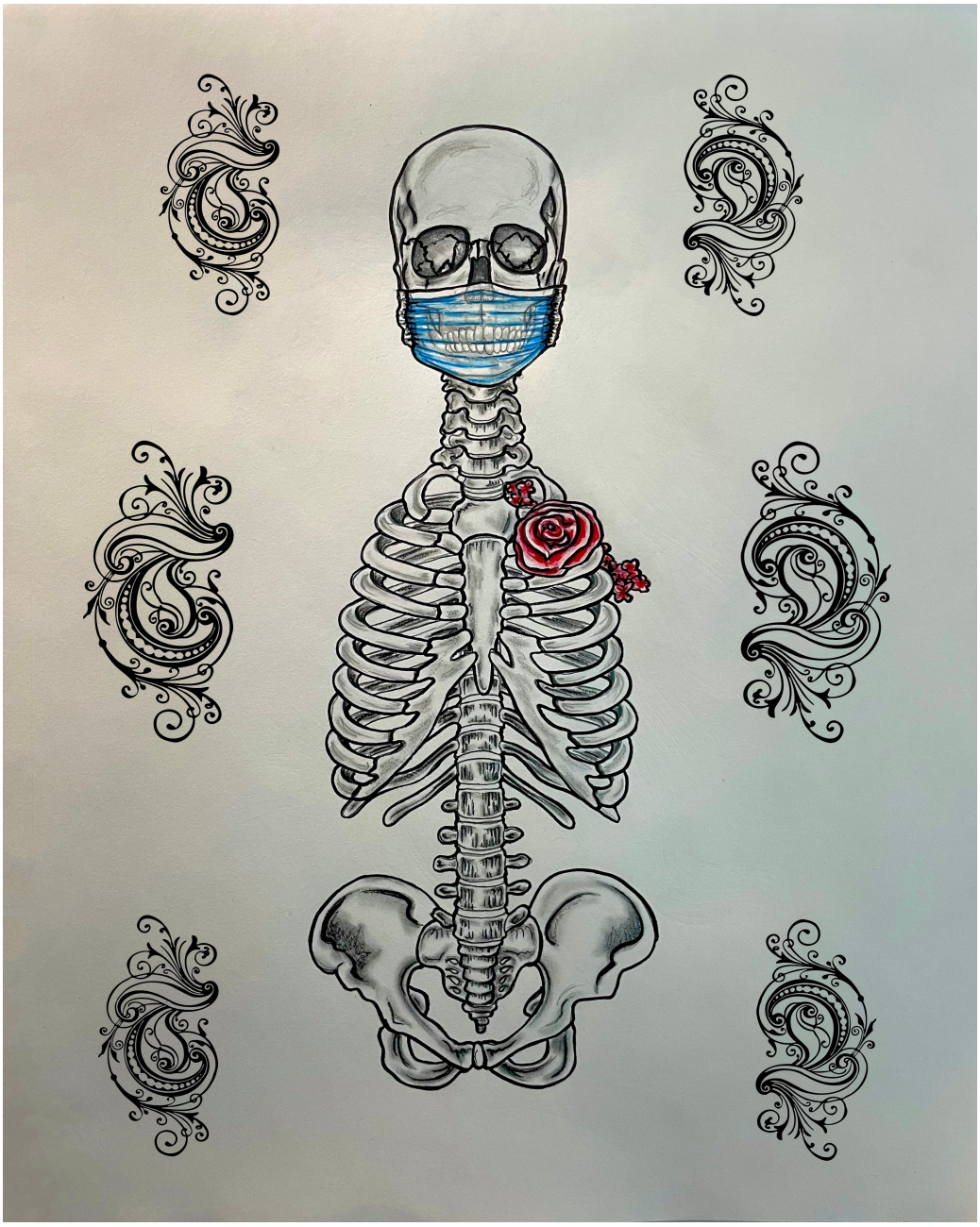
Hall 2012	New York City, US	Oral contraceptive	n=354 age=13-24 Setting: university-affiliated community-based clinic in New York City	This article found that 57% of their subjects reported weight change after 6 months (68% of which was weight gain). They noticed that those with depressed mood are twice more likely to report perceived mood and weight change compared to those without depressed mood. Young women who saw weight changes after 6 months of oral contraceptive use were 40% less likely to continue OC than without weight change. They claimed that perception of weight side effects can serve as a barrier to a contraceptive method.
Hall et al., 2013	New York City, US	Oral contraceptive	n=354 age=13-24 Setting: university-affiliated community-based clinic in New York City	This study found that while 57% of their subjects reported weight change after 6 months (68% of which was weight gain), the majority responded that weight change was "bad" and that weight change was attributed to the pill. They reported that weight change was associated with lower continuation rate, and the reported weight changes, weight gain, "a lot" of weight change was associated with lower continuation rate.
Hincapié-García et al., 2013	Madellín, Columbia	Hormonal contraception	n=353 age=17-30 Setting: University of Antioquia	A survey of University-level women in Columbia found that oral contraceptives were most commonly used, and that incidence of adverse events (48.6%) were associated with hormonal contraceptive discontinuation. Among those adverse events, weight gain (14.5%) and headaches (21.1%) were most prevalent.
Huda et al., 2014	Dinajpur, Bangladesh	Norplant	n=73 age=25-31 setting: Family Planning Association of Bangladesh	A questionnaire on Bangladesh Norplant users found weight gain (4.1%) as one of the reasons for early removal. 42% of the women were not informed of all of the disadvantages by their providers when choosing Norplant. The study also found that Norplant users may not have established trust with their providers as shown by the number of Norplant users who consulted with their husbands, family planning workers (31%), Norplant users (11%), and doctors (6.6%) for Norplant insertion.

Ibrahim et al., 2015	Kano, Nigeria	Hormonal contraception	n=334 age=3.72±3.2 setting=Murtala Muhammed Specialist Hospital antenatal care clinic	This article found that grand multiparous women in Nigeria most commonly used oral contraceptives and injectables. Major reasons for non-use, however, was cited as fear of side effects by 77.2% and desire for more children by 73.1%. Among the feared side effects included weight gain by 83.8%.
Kucuk et al., 2012	Aydin, Turkey	Combined oral contraceptive pills	n=418 age=18-49 Setting: Adnan Menderes University Hospital outpatient clinic	Interviews of Turkey women found that while 68.4% has never tried combined oral contraceptive pills (COCP), 45.2% of the participants believed in its cause of weight gain and 27.5% responded unsure about its effects on weight gain. While other studies have not shown much difference in weight gain from OCP and placebo, this study has shown the prevalence of misconception on COCP's cause of weight gain in Turkey women.
Lo & Fan, 2010	Hong Kong, China	Combined oral contraceptive	n=1295 age=18-45 Setting: online survey	An online survey of Hong Kong women found that among the 65% of women who have never tried combined oral contraceptives, 72.1% cited fear of side effects (including weight gain) as their primary reason. Similar pattern was examined among those who has discontinued their use of COC, with 27.9% citing the reason for discontinuation as weight gain.
Manharaj, 2012	KwaZulu-Natal, South Africa	Family planning methods	n=16 focus groups age=N/A setting= health facilities	This study found that South African women were afraid of weight gain because they have noticed acquaintances who appeared overweight after starting contraception. Other women reported discontinuing due to perceived weight gain. It was generally seen that unhappiness can result from severe side effects (weight gain).
Manzouri et al., 2010	Isfahan, Iran	IUD	n=11 age=15-49 setting= urban health center	The interviews from this study found that a common reason for non-use of IUDs was fear of side effects, including weight change. A participant answered that she has heard of IUD causing weight change and did not want that for herself as her husband would not like it. The study noticed that rumors and misperceptions about IUDs came from other IUD users.

Marvi & Howard, 2013	Karachi, Pakistan	Pill, injection, IUD	n=20 age=25-45 setting=Rana Liaquat Craftsman Colony health center	It was found that women believed in the heating effects of contraceptives, which in turn caused weight gain, menstrual irregularities, and weakness. Of the women who had used contraceptives, they also mentioned discontinuing or changing methods due to side effects. The study found that weight gain was thus associated with weakness and irregular bleeding.
Morotti et al., 2017	Italy	Nuvaring	n=21 age=18-35 setting=clinic	This study found that lean, young women on Nuvaring saw a very slight decrease in the averages of "satisfaction in body" and "feeling well with their own silhouette." Neither of these changes were statistically significant. The study also noticed that women perceived feminine figures as most attractive. No one discontinued from the method during the 6 month study.
Nanda 2018	Nairobi, Kenya	LARC (LNG-IUS)	n=29 age=18-49 setting=Family Health Options Kenya clinic	This article found that women chose LNG-IUD because they perceived that it would have less side effects such as weight gain. One of the participants perceived that there was less hormone and that hormones were localized in the cervix, thus not causing weight gain. Another participant was satisfied with the lack of weight gain after switching from another method that perceived weight gain.
Nault et al., 2013**	Missouri, US	LARC	n=1146 age=14-45 setting=university-based clinic, abortion clinics, community-based clinics	Women who received counselling about LARC followed up after their usage and 41% implant and 46% DMPA perceived weight change. Black race, lower SES, higher baseline BMI was associated with perceived weight gain. It was also found that implant and DMPA users were more likely to perceive weight gain than copper IUD users.
Ochako et al., 2015	Kenya	Modern contraceptive methods	n=34 age=16-24 setting=at homes	This study found in young women that weight change was cited as one of the most common fears of side effects. One of the women interviewed mentioned her belief on how injectables are bad because they make a lot of people notably fat. Study also noticed that 36% women reported discontinuation from the method during their first 12 months due to side effects.

Vogt & Schaefer, 2012	Germany	Oral contraceptives	n=51 age=18-24 setting=questionnaire	This study noticed women's negative association with weight gain with regard to COC. Women overestimated the risk of, and underestimated effectiveness of COC and many were even concerned about possible weight gain. The study also discovered that even physicians wrongly answered questions about common COC misperceptions.
Weisberg et al., 2013	Australia	Hormonal contraceptive	n=200 age=18-50 setting=online survey	An online survey of women and general practitioners in Australia found that least attractive features of hormonal contraceptives include: weight gain of 3kg; painful, heavy, and irregular periods; high cost; and low failure rates.
Williamson et al., 2009	Scotland	LARC	n=20 age=20 setting=homes	The interview conducted in this study found that the 4 out of 20 interviewed have tried progestin-only-pill or injections and all have discontinued due to experienced side effects. One of the participants noticed weight gain in her friend from injections, and thus did not want to use it herself. Women who were on injectables noticed substantial weight gain and thus cited weight gain as a reason for discontinuation.

NARRATIVE REVIEW



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NARRATIVE REVIEW
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Congenital Cytomegalovirus Infection: Transmission, Diagnosis and Treatment

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ABSTRACT

Introduction: Cytomegalovirus (CMV) is a linear, dsDNA virus that is regarded as the prototype of the *Betaherpesvirinae* subfamily of viruses. It has an established endemic status in certain locations around the globe and is also reported to be the most prevalently occurring congenital infection in humans. Furthermore, Cytomegalovirus is notorious for being a persistent lifelong pathogen that poses a threat of reactivation as well.

Discussion: Congenital cytomegalovirus infection causes numerous ophthalmologic, and neurologic sequelae, and is also known for being the principal reason behind sensorineural hearing loss of non-genetic etiology in neonates. These symptoms, if present, may give rise to a premonition of congenital Cytomegalovirus disease, and so, a diagnosis can be established through serology, radiology, and PCR of salivary, urinary, or dried blood spot samples. Timely administration of ganciclovir or valganciclovir has proven to be effective in managing symptomatic cases of congenital CMV.

Conclusion: A well-timed delivery of pharmacological and non-pharmacological interventions is necessary to achieve healthy developmental outcomes for the neonate. Moreover, there is still a need to study the role of antiviral therapy in silent cases since asymptomatic patients are at risk of developing long-term clinical sequelae as well.

Relevance: An estimated 60-90% of women of child-bearing age get infected with Cytomegalovirus, and Congenital CMV disease is reported in 0.2-2.4% of all live births. Therefore, in order to develop effective screening and management protocols, it is vital to educate healthcare professionals regarding the various aspects of this congenital infection.

KEYWORDS

Congenital, Cytomegalovirus, Infection, Hearing loss

1 | INTRODUCTION

Cytomegalovirus, also known as the Human betaherpesvirus 5, is a pathogen that is indexed under a family of viruses known as the '*Herpesviridae*', and it is also regarded as the prototype of the *Betaherpesvirinae* subfamily. Its linear, double-stranded(ds) DNA genome is considered to be one of the largest amongst the other human viruses; and, possessing a length of approximately 235kbp, it is also recognized as the largest genome amongst the human herpesviruses. (1) CMV is unanimously accredited as the most prevalently occurring congenital infection in humans. It is reported to infect 60-90% of women of child-bearing age in various parts of the world. (2) The global circumstances surrounding CMV infections are recognized as being of an endemic nature owing to the understanding that CMV infections fester in most of the human populations. (2) Moreover, the seroprevalence of CMV is generally subject to the socioeconomic status of the affected area. Therefore, incidences reaching a maximum of 100% may be observed in underdeveloped locations. (3) CMV mainly causes an asymptomatic primary infection in immunocompetent people but may manifest as a severe focal disease having various clinical symptoms in immunosuppressed individuals. As observed with other herpesviruses, the phenomenon of latency and reactivation is also prominently discerned in cases of CMV infection. Therefore, persistent lifelong infection with the risk of potential reactivation on encountering a breach in the immune defense mechanisms is a characteristic clinical challenge associated with these viruses. (3)

This review aims to explore the various aspects of congenital CMV infection including transmission, clinical manifestations, diagnosis, and treatment. Moreover, while discussing these facets, a primary focus will remain on the recent diagnostic and therapeutic developments recorded in the literature.

2 | TRANSMISSION

Primary CMV infection in a healthy individual is generally silent but the shedding of the virus may persist through urine, saliva, and blood. Therefore, the spread of the virus is maintained through sexual and nonsexual contact. (4) Intimate degrees of contact with an infected individual capable of potentially expelling the virus through their bodily secretions appears to be the primary mechanism of horizontal CMV transmission. (5) Transplantation of an organ-harvesting latent CMV and transmission of CMV through blood transfusions in immunosuppressed individuals can result in a life-threatening disease as well. (5) However, it appears that monocytes serve as prime vectors for latent CMV and, hence, the transfusion of leukocyte-reduced blood can lower the incidence of transfusion-transmitted CMV disease in immunocompromised individuals. (6)

Moreover, vertical transmission plays a pivotal role in maintaining a sustained incidence of human CMV infections. Mothers who are infected during or even before pregnancy can transmit the infection to their child. Three routes of vertical CMV transmission have been primarily described, (7)

1. Transplacental route during the intrauterine period
2. Through breast milk
3. Intrapartum route

It should be noted that only transplacental route of CMV transmission results in a congenital infection while intrapartum and postpartum transmission does not cause congenital CMV disease.

The frequency of transplacental transmission of CMV varies with the gestation period. The rate of transmission progresses from a lower incidence of 20% to a higher incidence of 75% if the primary infection is contracted during the first and third trimester respectively. (7) Furthermore, congenital CMV disease as a consequence of first-trimester maternal infection, is more likely to manifests as a symptomatic case at birth with the possibility of resulting in long term disabilities. (8, 9) Additionally, it should be noted that previously acquired maternal immunity against CMV is not always efficacious in preventing congenital CMV in the neonate. Evidence exists to suggest that maternal reinfection with a CMV strain possessing a slightly different epitope

could potentially explain why children of women with past immunity would develop the congenital CMV infection. (10) Hematogenous spread of infected leukocytes across the placental barrier, and local infection of the placenta and amniotic fluid are mechanisms that describe the transplacental spread of CMV. (11)

Additionally, reactivation of CMV is observed in 96% of the seropositive lactating women, and the infectivity of breast milk can be established 3 days post-delivery. (12) There have been reports in the literature to suggest that postnatally acquired CMV infections can yield severe consequences in some premature infants. (13-15) Therefore, efforts have been made to develop techniques that can aid the removal of CMV from milk while also conserving its beneficial elements. Processes to treat the milk at high temperatures (72°C) for a short duration of time (5 seconds) have proven to be somewhat effective in achieving the desired degree of preservation. (16) Alternatively, milk donated by seronegative lactating women can also be utilized to avoid the potential risks of losing the health-giving properties of colostrum when subjected to such treatments. (17)

3 | CLINICAL MANIFESTATIONS OF CONGENITAL CYTOMEGALOVIRUS INFECTION

An estimated 0.2-2.4% of all live births suffer from a congenital infection of cytomegalovirus. (18) Additionally, congenital CMV infection is reported to be the most common non-genetic reason behind sensorineural auditory impairment and delay in neurological development in children. (18) About 90% of the newborns infected with CMV have a clinically silent infection and show no perceivable symptoms or signs. (18) However, up to 56% of these apparently asymptomatic patients may have laboratory, ophthalmologic, or neuroimaging findings that would recategorize them as symptomatic cases when evaluated. (18) Therefore, a well-oriented, thorough and targeted screening approach is necessary so as to not miss any instances of infection in the apparently healthy neonates. (18)

Infants with asymptomatic CMV infection may not have the typical physical or neurodevelopmental abnormalities, (19) but the literature reports that up to 23% of these asymptomatic children may experience sensorineural hearing loss, (20) which can hinder their normal linguistic and cognitive development. (21)

Hearing impairment, hepatomegaly, splenomegaly, petechial rash, thrombocytopenic purpura, jaundice, growth retardation, chorioretinitis, and cataracts are some of the presenting signs observed in a neonate suffering from congenital CMV disease. (22) Moreover, a placenta that is 3-folds greater in size than average has also been observed if the neonate has acquired the congenital CMV infection. (23)

3.1 | Laboratory Findings

An increase in serum transaminases, decreased platelet count, and increased serum concentration of conjugated bilirubin are the most frequently occurring laboratory manifestations of congenital CMV infection. (24) Platelet counts below 50,000/µL have been observed in 1/3rd of the symptomatic patients. (25) CMV-related thrombocytopenia may be observed due to the destruction of platelets via autoimmune mechanisms, bone marrow dysfunction, or the consumption of platelets as a result of disseminated intravascular coagulation. Furthermore, bone marrow dysfunction or hemolytic destruction of blood cells may also result in mild anemia. Polychromasia, increased reticulocyte count, and RBCs possessing nuclei, are some indications suggestive of a hemolytic etiology. Moreover, bone marrow examination may reveal a decreased erythrocyte precursor count if the virus induces bone marrow inhibition as well as, an elevated erythroid to myeloid ratio is detected in circumstances of hemolysis. (25) It has also been reported that 50% of the symptomatic CMV patients may have elevated cerebrospinal fluid (CSF) proteins with lymphocytic pleocytosis and CMV may even be detectable in the CSF of these patients. (25, 26)

3.2 | Sensorineural Hearing Loss

The sectional temporal bone analysis during the autopsy examinations of children suffering from congenital CMV infection has revealed the presence of viral inclusion bodies throughout the inner ear. (27) Diffusely present viral inclusion bodies have been discerned in the basilar membrane, cochleovestibular ganglion, Reissner's membrane, and spiral ligament. Destruction of the inner hair cells along with the outer hair cells has also been detected and so, a few theories have tried to explain the reasons behind the loss of these cell populations responsible for the transduction of auditory signals. Inflammatory response of inner ear to CMV, direct infection of the hair cells, or CMV mediated destruction of stria vascularis are possible mechanisms operating behind the loss of hair cells and ultimately, behind the sensorineural auditory impairment associated with congenital cytomegalovirus infection. (28)

CMV-associated hearing impairment can be a finding detected at birth or it may even be identified later in life owing to a delay in its onset. Up to 50% of sensorineural hearing loss (SNHL) due to congenital cytomegalovirus infection is delayed-onset loss of hearing, and almost half of these patients experience progressively deteriorating auditory function. (29) Late onset hearing loss due to congenital CMV infection may occur a few years after birth, and a delay of 11 months in the onset of SNHL is generally observed in asymptomatic patients compared to the symptomatic cases. (29) Therefore, children with congenital CMV infection should have a periodic evaluation of their hearing until the age of about 6 years. (29). It is documented that approximately 5% of the asymptomatic patients develop at least unilateral SNHL within 12 months of being born. (30) CMV-related congenital sensorineural hearing loss is generally not observed if the maternal infection occurred during the 3rd trimester of pregnancy. While, 80% of the children born to mothers primarily infected in the first trimester had sensorineural auditory impairment at birth. (31) It is, however, interesting to note that fluctuation in the sensorineural hearing loss is a factor independent of the gestation period. (31)

Vigilant identification of auditory impairment early in life, and initiation of nonpharmacological interventions within a few months can substantially aid linguistic, social, behavioral and emotional child development. (32) Ideally, the recognition of hearing impairment and appropriate intervention should begin before 6 months to achieve desirable degrees of child development. (33) Healthier child developmental outcomes are also vital in relieving parental stress and maintaining a nourishing parent-child interaction. (32)

3.3 | Ophthalmologic Manifestations

Approximately 5-30% of patients with congenital CMV disease have ophthalmologic manifestations. (34) Results of a long-term prospective study have highlighted that 78% of the symptomatic congenital CMV patients had normal vision compared to 98.8% of the asymptomatic cases. (34) 1.2% of the patients in the asymptomatic group had moderate vision loss caused by macular scarring while 17% of the symptomatic patients had severe vision loss owing to cortical blindness or optic atrophy. (34) Ocular lesions of congenital CMV disease can be categorized as per the anatomical structures of the eye. It has been estimated that the lesions of anterior segment of the eye are not usually a consequence of congenital CMV infection. (34) This finding hints towards the minimal capacity of the cytomegalovirus to affect non-neuronal cellular lineages. (34) Moreover, the posterior segment of the eye and the cortical visual pathway are accounted as the potential sites for CMV action in children. (34) Chorioretinitis, optic atrophy, strabismus, and visual cortex lesions are the abnormalities that are most frequently detected, (34) and optic atrophy as well as cortical visual impairments have been reported to be the most frequent causes of bilateral visual defects in such patients. (35) Additionally, it should be noted that active cases of CMV-related retinitis can present with or without hemorrhagic manifestations. (35) Since ocular developmental abnormalities can also be seen as a consequence of congenital CMV infection, a targeted investigation of all severe developmental abnormalities of the eye might appear necessary but is generally not

required unless other clinical signs of congenital CMV disease are also present. (35)

3.4 | Neurologic Manifestations

It is generally perceived that symptomatic cases of congenital CMV infection are associated with poor neurological outcomes in the patient. However, a study has reported that 59% of the children suffering from symptomatic congenital CMV infection had a normal Intelligence Quotient (IQ). (36) However, microcephaly has been reported to be a firm indicator of poor cognitive developmental outcomes in a child suffering from congenital CMV infection. (36) Similarly, lissencephaly and pachygyria are also linked to more severe neurological disabilities as compared to polymicrogyria. (37) Some of the other neurological presentations may include lethargy, seizures, hypotonia and poor oral feeding. (24) It has been estimated that neurological impairments are detectable in 6.5% of the asymptomatic patients and a total of approximately 8000 children in the US suffer from CMV-related neurological impairments each year. (37)

A neuropathogenic model hypothesizing the development of neurologic manifestations of CMV has been proposed by studying the spread of CMV particles in the brain of mice. CMV initially causes meningitis and choroid plexitis by diffusing out of the meningeal and choroidal vessels. (38) This spread, in turn, leads to a blood brain barrier disruption, and therefore, cytomegalovirus particles further spread to infect the ventricular and subventricular zones where the virus induces a neural cell loss by blocking the proliferation and differentiation of neural stem progenitor cells. (38)

3.5 | Findings on Neuroimaging

Bedside ultrasound, MRI, and CT scan are the imaging technologies employed in order to obtain an elaborate evaluation of the newborn suspected of having congenital cytomegalovirus infection. Ventricular size determination, as well as the visualization of periventricular calcifications can be achieved with the aid of ultrasound technology. Periventricular calcifications along with neuronal migration abnormalities are among the classical findings discerned in a patient of congenital CMV infection, and these abnormalities also serve to differentiate congenital CMV infection from other congenital diseases. Ultrasound can be appropriately utilized as the first imaging procedure in symptomatic children and it serves as a reasonable technique for predicting the outcomes in such patients as well. (39) Furthermore, head CT scan provides a more detailed image that is beneficial in effective localization and depiction of the cranial manifestations such as calcifications. (37) Cerebellar hypoplasia, polymicrogyria, lissencephaly, schizencephaly, ventriculomegaly, and cortical dysplasia are some of the neurodevelopmental manifestations that can be visualized effectively using MRI technology. (37) However, ultrasound may be more effective in the visualization of periventricular calcifications (even prenatally) as compared to an MRI. (37)

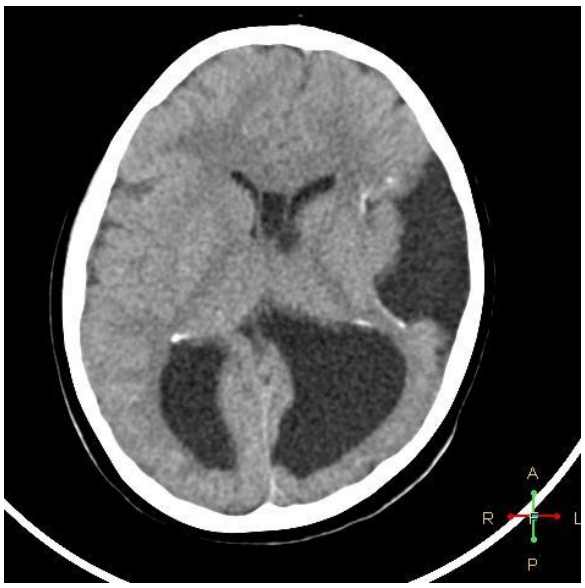

FIGURE 1 10-year-old male presented with delayed mental and motor milestones. Axial non-contrast computed tomography scan shows hydrocephalus with periventricular calcification, pachygyria, and cavum septum pellucidum.
Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 24282.

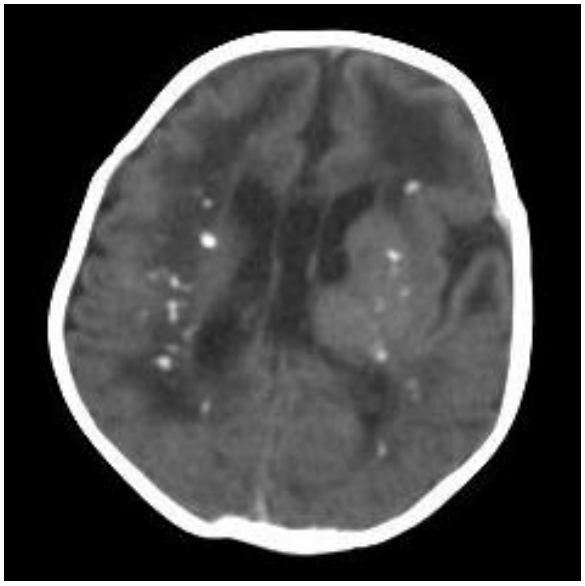

FIGURE 2 Computed tomography scan of a 2-month-old male showing scattered periventricular and basal ganglia calcification. These findings may be indicative of congenital cytomegalovirus infection.
Case courtesy of Dr Aneesh KM, Radiopaedia.org, rID: 17105.

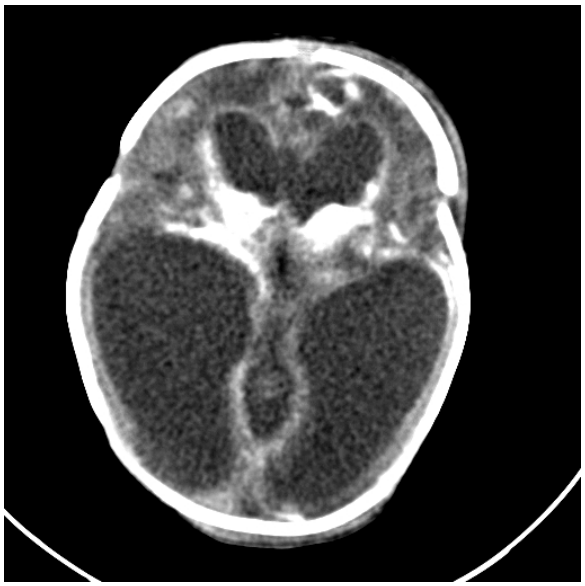

FIGURE 3 1-day-old male has scalp swelling and a weak cry. Extensive periventricular, basal ganglionic and parenchymal calcification with hydrocephalic changes and parenchymal atrophy can be seen on the computed tomography scan.
Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 29095.

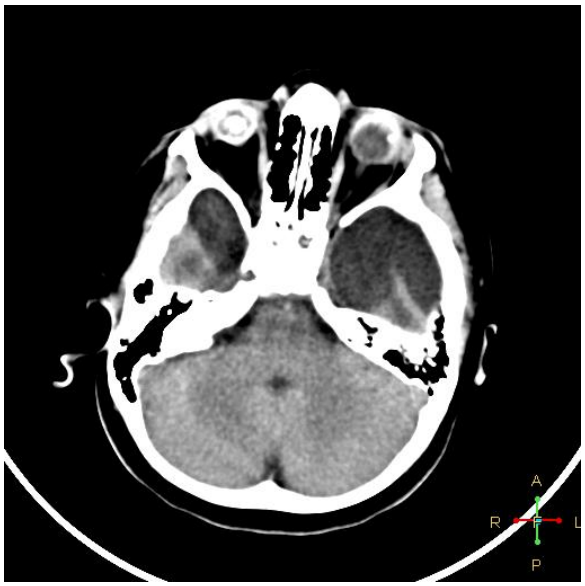

FIGURE 4 10-year-old male presented with delayed mental and motor milestones. Axial non-contrast computed tomography shows right microphthalmia and bilateral chorioretinal calcification.
Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 24282.

4 | DIAGNOSIS

Congenital CMV is a clinically significant infection that prevails substantially and is also documented under notorious terms for its long-term sequelae that can potentially hinder the normal development of children. Despite the incidence associated with congenital CMV infection, cases often go unidentified due to asymptomatic manifestation or nonspecific symptoms at birth. As discussed earlier, late-onset sequelae such as SNHL can be observed in both symptomatic and asymptomatic patients, highlighting the need for a post-natal screening protocol for congenital cytomegalovirus infection. The development of a screening protocol mostly relies on the clinical manifestation of a disease, but due to its potential asymptomatic presentation, an evident risk of missing the majority of the congenital CMV cases is highlighted to be problematic. Therefore, emphasis has been made recently on the need for a universal screening protocol. Currently, a lack of recommendations and effective implementation of appropriate

universal neonatal screening protocols are observed in many countries, (40) since most asymptomatic cases of congenital CMV do not lead to clinical sequelae, and a diagnosis of congenital CMV infection could unreasonably stress the parents. Moreover, a lack of treatment options available to prevent sequelae in asymptomatic group makes the implementation of a universal screening protocol even more difficult. However, it is worth mentioning that Ontario, Canada has implemented universal screening for CMV as part of their Infant Hearing Program, and a study has also indicated the feasibility of upscaling the Australian pilot CMV screening program into a universal newborn hearing screening (UNHS) program. (41)

Universal CMV screening of neonates has yet to find implementation in most countries but efforts to study and implement targeted screening of neonates who fail the audiological screening examination have proven to be beneficial and cost effective to some extent in the United States, United Kingdom, Belgium, and Australia, (42-45) however such targeted screening can miss the majority of the asymptomatic cases.

Maternal CMV testing is usually indicated after uncovering suspicious fetal ultrasound findings such as fetal ventriculomegaly, growth restriction, cerebral calcifications, and echogenic fetal bowels. (46) Therefore, universal maternal screening for CMV is not recommended unless suspicious pre-natal ultrasound findings are reported. Similarly, symptoms of primary CMV infection in the pregnant women can also serve as an indicator for maternal CMV testing.

Maternal testing for CMV immunoglobulin M (IgM) is the most prevalently deployed investigation to detect primary maternal infection, but IgM may even be positive in cases of reinfection or reactivation. CMV IgM peaks in the initial 1-3 months and may persist for up to 12 months. Moreover, false positive IgM results are not infrequent in the presence of some other autoimmune pathology or viral infection. Due to the difficulties associated with interpreting IgM results, serum immunoglobulin G (IgG) avidity can be a beneficial investigation to differentiate between primary maternal infection and reinfection or reactivation. Avidity testing of antibodies detects the strength of binding between the polyvalent antibody and the antigen. Serum IgG detected up to 18 weeks after a primary maternal infection has a low to moderate avidity, while high avidity IgG may persist for years. (46) Therefore, high avidity is only detectable in past CMV infections. When jointly interpreted, low avidity of maternal IgG, and detectable IgM in the mother's blood can be firm indicators of a positive primary maternal infection. (46) Hence, it is not recommended to base the diagnosis of primary CMV infection solely on a detectable IgM, since avidity testing of IgG appears to be necessary to diagnose a primary maternal infection acquired within the past 3 months. (46)

Saliva and urine are the ideal samples to detect the presence of CMV in a neonate, however, oral swabs are preferred over urine samples merely due to convenience in their collection. (47) CMV polymerase chain reaction (PCR) is now increasingly preferred over CMV cultures for screening and diagnostic purposes and PCR testing of saliva has also been validated as an appropriate screening method. (47) Timely collection of these samples is crucial to detect congenitally acquired CMV, since positive CMV indications in samples collected 3 weeks post-delivery may represent a postnatally acquired infection which is usually not associated with significant clinical sequelae. (48) Similarly, false positive results can also be seen if the salivary sample is taken after the child is recently breastfed but it is important to note that the rate of false positive results with salivary samples is still reported to be considerably low. Additionally, stored and dried blood spots obtained at birth can also be useful to retrospectively diagnose a congenital CMV infection, but the sensitivity of this technique is documented to be significantly lower than the one for PCR testing of salivary samples. (48) Moreover, only 80-90% of the newborns with congenital CMV disease have the virus particles in their blood soon after birth, therefore a negative dried blood spots test cannot completely rule out congenital Cytomegalovirus disease. (48) Undetectable cytomegalovirus-specific IgG effectively discounts the probability of a congenital infection. (47) Serum IgM level of an infant has a low sensitivity in diagnosing congenital CMV infection, but an elevated level of serum

IgM can serve as an indicator for symptomatic disease, thus encouraging the healthcare providers to aptly initiate further investigations for such patients. (49) However, it should be noted that serum IgM testing has no utilization in ruling out symptomatic disease. (49)

Prenatal identification of CMV is equally crucial to plan potentially necessary therapeutic measures and to also provide timely informational care regarding the potential risks of congenital CMV infection to the family. Amniocentesis for the detection of CMV DNA is the most effective tool in diagnosing congenital CMV infection prenatally. (50) This diagnostic amniocentesis should be performed ideally after 21 weeks of gestation and 6 weeks after the primary maternal infection. (46) Risk of a false negative result has been reported if the amniocentesis is performed prior to the 21st gestational week. (46)

5 | TREATMENT

Antiviral therapy for congenital CMV infection is only indicated in symptomatic cases and treatment of asymptomatic cases at birth has not shown to reduce SNHL later in life. Numerous developments have been recently recorded to establish the utilization of ganciclovir and oral valganciclovir for the management of symptomatic congenital cytomegalovirus cases. According to the results of a randomized control trial, early administration (within 1 month) of ganciclovir at a dose of 6mg/kg administered twice daily for 6 weeks, demonstrated hearing improvement at 6 months and also successfully prevented further deterioration in hearing. (51) Similarly, improvements in neurodevelopment at 6 months and 12 months have also been suggested with the use of ganciclovir. (52) However, a momentous proportion of ganciclovir-associated hematotoxic adverse effects have been documented in these patients. 63% of the trial subjects developed severe neutropenia during treatment, (51) and even further, toxicity of the gonads and carcinogenic properties of ganciclovir have also been studied in animal subjects. (51)

Oral valganciclovir has established a comparable efficacy to ganciclovir with fewer adverse effects and convenient administration, but valganciclovir has not proven to be beneficial in improving short term hearing outcome for symptomatic congenital CMV patients. (53, 54) However, 16mg/kg of valganciclovir administered twice daily for 6 months did improve long term hearing and neurodevelopmental outcomes. (54) Furthermore, there have been two cases reporting effective utilization of Foscarnet in the management of congenital cytomegalovirus disease. (55) The use of foscarnet in congenital infections of CMV still lacks support to establish the efficacy of this drug in the pediatric population. (55) However, foscarnet is still considered to be the second line agent for pediatric neurological and herpes simplex virus infections. (55)

The treatment of congenital CMV patients presenting with isolated SNHL at birth has been a topic of controversy and general recommendations suggest against the use of antiviral therapy in such patients due to insufficient evidence. The results of a recent uncontrolled observational study have reported significant benefit of long-term antiviral therapy in patients with isolated SNHL. (56) The data from this study has also recorded no deterioration of hearing outcomes in the unaffected ear. (56) Interestingly, 8g/day of valaciclovir in pregnant women has also shown promising results in preventing transplacental CMV transmission after primary infection of the mother in the first trimester. (57) Implementation of this treatment strategy could limit symptomatic cases of congenital CMV infection.

6 | CONCLUSION

Congenital CMV infection is a clinically significant infection with a worldwide scope of prevalence. It is the principal non-genetic cause of sensorineural auditory impairment in children, and its symptomatically variable presentations pose an important challenge for clinicians since initial asymptomatic cases can also lead to debilitating sequelae months after birth. Various laboratory, ophthalmologic, and CNS findings can aid in the clinical identification of congenital CMV disease, and so,

emphasis should be made on the accurate and timely diagnosis of this infection. Aptness in the diagnosis can help ascertain a well-timed initiation of the pharmacological and non-pharmacological interventions to aid the developmental outcomes of the child. Furthermore, ganciclovir, and valganciclovir can be administered after a risk-benefit evaluation of the patient. However, studies indicating the advantages of antiviral therapy, in the management of congenital CMV disease, have only highlighted therapeutic interventions concerning symptomatic cases, and there is still a lack of studies that focus on the therapeutic outcomes of these medications in asymptomatic patients and in patients with isolated SNHL. Therefore, a detailed study of the various aspects concerning asymptomatic congenital CMV infection is required. As of now, the use of antiviral medications is not indicated in silent CMV infections and treatment protocols may not even be investigated until indicators of debilitating clinical sequelae are established in these patients.

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NARRATIVE REVIEW
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Epistemic and Ethical Considerations in the Direct-to-Consumer Health and Ancestry Genetic Testing Process

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ABSTRACT

Background: Direct-to-consumer genetic testing (DTC-GT) is a popular and fast-growing field within the healthcare industry. Consumers often pursue DTC-GT without a clear understanding of its epistemic and medical limitations. This report will present the current state of DTC-GT technology, and highlight the ethical, legal and social issues of DTC-GT.

Methods: Quantitative sources such as systematic reviews were used to evaluate the field of DTC-GT. Experimental data was taken from randomized control trials and case studies of 23andMe. Qualitative sources such as newspaper articles and surveys were also used. Relevant policies and regulatory information were analyzed in the context of 23andMe as a case study. Broader ethical issues are analyzed from the social disability model and feminist ethics frameworks.

Results: Several aspects of direct-to-consumer genetic testing are outlined: (i) regulatory and legal distinctions of DTC-GT that separate its use from conventional genetic testing, (ii) epistemic issues of the genetic testing process within the direct-to-consumer context, and (iii) ethical considerations of DTC-GT regarding genetic health and genetic ancestry.

Conclusion: This report does not take a position for or against the use of DTC-GT; rather, it highlights the key ethical issues often missed in the DTC-GT process. There is no perfect method for understanding genetic health and race. DTC-GT offer consumers the ease and power of taking genetic data 'in their own hands', at the cost of exacerbating geneticization and race essentialism. Until further work is done to address the epistemic, regulatory and legal issues, ethical implications of DTC-GT usage will continue to exist.

KEYWORDS

Direct-to-consumer, Genetic testing, Ethics, Epistemology, Guideline

1 | INTRODUCTION

This report aims to provide an ethical framework on direct-to-consumer genetic testing (DTC-GT) of health and ancestry genetics for stakeholders and individuals interested in the DTC-GT process. Findings suggest that epistemic issues in health and ancestry genetic data interpretation lead to ethical consequences of geneticization (1) and race essentialism (2), respectively. The ethical analysis will be centered on the case study of 23andMe, a US-based DTC-GT company. A brief overview of the DTC-GT process will be presented, alongside an epistemic analysis of its scientific validity. The discussion will be linked to the broader ethical consequences of geneticization and race essentialism, analyzed using a social disability and feminist ethics framework. This report does not take a position for or against the use of DTC-GT; rather, it presents a clear framework of ethical considerations for the consumer to interpret. Alternatives to DTC-GT will be proposed, such as clinical genetic counseling, epigenetic sequencing and metagenomic sequencing. Ultimately, DTC-GT will be contextualized within the greater scope of molecular screening technologies and the field of bioethics.

2 | METHODS

This paper draws on quantitative sources such as systematic reviews to report the field of DTC-GT. Clinical data was taken from randomized control trials and case studies of 23andMe which fulfilled ethics approval. (3-13) Qualitative sources such as newspaper articles and surveys were also used. (14-18) The sources were retrieved through a query search on Google Scholar and PubMed in November 2020. The keywords used in the search were: direct to consumer, genetic testing, 23andMe, ancestry, health, ELSI, ethical, legal, social, epistemic, issues, interpretation, consumer, legal, policy, terms of use. Relevant policies and regulatory information were analyzed in the context of 23andMe (19-24) as a case study intended to represent the process of DTC-GT for an average consumer. Claims about 23andMe were cited from the company website, policies, and terms of use. Broader ethical issues are analyzed from the social disability model and feminist ethics frameworks, defined as:

- *Social disability framework* (25): that the conception of 'disease' is not a product of genetic or clinical anomalies, but a product of barriers and lack of (medical/political/social) accommodations that render an individual 'disabled' within their specific social context.
- *Feminist framework* (26): that the individual is situated within a social web of intersectional relationships, and power hierarchies are maintained through existing social structures.

3 | DISCUSSION

3.1 | 23andMe, and epistemic problems of direct-to-consumer genetic testing

3.1.1 | Regulatory and legal distinctions of DTC-GT

DTC-GT refers to the branch of commercial services offering personalized sequencing and analysis of individual DNA. Testing services can reveal either ancestry (via genealogy or racial breakdown) or health (via genetic markers or health traits) information, or both, by sequencing genomic DNA. (19) This service can be offered by a private company (such as 23andMe) after paying an upfront fee. It is important to understand the context DTC-GT operates under, as several aspects distinguish it from the clinical genetic counseling practices people may be used to. For example, legally speaking, the individual is not considered to be a patient but a *consumer* (20,27). In other words, the process is generally seen as the purchase of a consumer good and not a regulated health service. This legal distinction forms the basis for how consumer data is analyzed and protected. DTC-GT might be advertised to be scientifically informative, but they may not be legally considered a diagnostic tool. (3) In other words, consumers should look to DTC-GT for

recreational and not diagnostic purposes. Any company that markets their tests as a diagnostic tool without the legal jurisdiction over-promises their scope of regulatory and legal protection to consumers.*(3)

Clinically speaking, this service does not operate under the regulatory guideline of a professional medical order (4), and thus may lack third-party harmonization and regulation in terms of conduct. DTC-GT allows the consumer to bypass administrative barriers associated with the ordered healthcare system, culminating in a faster and more autonomous experience of genetic testing. (27) Typically, genetic testing under the clinical setting requires a physician's referral and genetic counsellors to interpret the information, which typically takes months to proceed. (3) For DTC-GT, standardized procedures allow the entire process to be completed in a 3-5 weeks from the time of purchase. (28) The trade-off for speed, ease-of-access, and autonomy in DTC-GT is a compromise in regulatory policies that serve to protect individuals. For example, informed consent should be explicitly obtained and maintained during the entire clinical process, while consent in DTC-GT may be ambiguously presented or obtained only once at the time of purchase. (29) Consumers should be aware that these subtle differences in regulatory and legal practices impact the way their genetic data is stored, processed and interpreted. Thus, the decision to undergo DTC-GT entails more than just purchasing a service.

3.1.2 | Epistemic issues of the DTC-GT process

When a DTC-GT test is ordered, consumers are sent a testing kit to collect their DNA, such as a saliva sample in the case of 23andMe. (19) The sample is sent to a testing center where high-throughput (HTP) sequencing technologies are used to amplify, read and record specific parts of DNA sequences in parallel. (5) The sequences are then transferred to a computer database and 'analyzed' by comparing the individual sequence to a 'reference genome' composed of healthy individuals from a variety of racial backgrounds. (5) Thus, the 'interpretation' aspect of DTC-GT relies on pre-established standards as the reference point of comparison, removing the need for a genetic counsellor to interpret test results on an individual basis. In this sense, DTC-GT consolidates the sequencing and interpretation process of genetic screening into one mass-produced service. (19) The genomic differences of individual consumers are not analyzed from a personalized perspective but compared across a generic standard.

The interpretation of DTC-GT data poses epistemic issues regarding the scientific validity of what the tests claim to reveal. (14) Firstly, 23andMe markets a broad and in-depth analysis of DNA. (19) In reality, the entire human genome is not sequenced – due to the limitations of HTP sequencing technologies and the enormity of the human genome, such a feat is costly, time-consuming and outside the feasibility of a commercialized company aiming at rapid genetic results. (30) Instead, only a selection of single nucleotide polymorphisms (SNPs) is sequenced within DNA.†(30) This process is what 23andMe calls 'qualitative genotyping' (21): selecting clinically relevant variants in various parts of genomic DNA, then associating a particular SNP to some disease or ancestry lineage. It is qualitative because the process relies on human cognition to determine which exact SNP to select for, and what effect it has on a given health/ancestry outcome. In other words, the interpretation of SNP variance depends on the subjective interpretation of the company's genetic counsellors and data analysts.

Moreover, the way that 23andMe advertises qualitative genotyping presumes that SNP variance is a direct agent of disease or ancestry. (31) Such a claim is under epistemic contention as basic research is constantly challenging the causal perception of genomics. Furthermore, it is not always the case that a particular SNP variant (genotype) produces a certain health/ancestry state (phenotype), or that a particular phenotype is due to genetic abnormalities (it could also be due to issues at the epigenetic, RNA, or protein level, for example). (31) It could also be the case that the true genomic 'cause' was missed entirely by the company's analytical process, due to a lack of SNP selective pressure or scientific knowledge. (31) Thus, any marketing claim which purports to

advertise a comprehensive or objective view of genomic analysis is misleading, as only a fraction of the genome is examined, and the results are largely filtered by a selection bias of known SNPs only. (32)

In the case of health data, the individual's SNPs are compared to the SNPs of the reference genome in order to determine if the individual is a carrier for a particular disease. (22) If an anomaly is detected, it simply means the individual has a mutation or allelic variant that does not exist in the reference genome. (30) As correlation does not imply causation, it is important for the consumer to understand that 'disease status' of a DTC test result does not mean the consumer will necessarily develop the disease itself. This distinction is made clear in the fine print of a DTC company's legal regulations. Although 23andMe's 'Genetic Health Risk' and 'Carrier Status' tests advertise meeting the criteria for being scientifically and clinically valid, their legal policies also claim that:

> *"The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment. Our carrier status reports can be used to determine carrier status, but cannot determine if you have two copies of any genetic variant. These carrier reports are not intended to tell you anything about your risk for developing a disease in the future, the health of your fetus, or your newborn child's risk of developing a particular disease later in life." (19)*

Therefore, the health tests should not be seen to claim any more than a qualitative interpretation of SNP variance. DTC-GT companies like 23andMe may use vague marketing of their diverse SNP variants to obscure this point(4). For example, 23andMe advertises their tests to be "clinically and scientifically valid" (19), and yet in fine print, they disclose that not all health reports are FDA approved, nor are the tests intended to reveal a person's state of health, determine carrier status, or assess the risk of developing a certain disease. (24) In reality, SNP variance should not be seen as more than a *correlation* to health/ancestry. DTC-GT companies could do more to clarify this epistemic distinction, instead of listing it as fine prints and footnotes in their policies.

For ancestry analysis, the similarity of the individual's SNP haplogroup is compared to the SNP haplogroups of 14,437 people with known ancestry in the 23andMe database. (23) Ancestry data is found by comparing individual sequences to other individuals in the database, while racial breakdowns are tracked in correlation with historical human migration of distinct ethnic groups. (23) The specific percentage of racial or ancestorial breakdown is thus determined based on what proportion of a consumer's DNA matches some individual or group reference genome. (23) There are three types of sequencing (autosomal, mitochondrial, and X/Y-chromosomal) that 23andMe employs. (23) While each type sequences a different part of the genome, all methods face various degrees of contention regarding its scientific validity. Ancestral testing requires a higher degree of qualitative interpretation than genetic health data, as the reference genome is based on a qualitative determination of perceived 'race' to geographical locations. (33) As empirically hard as it is to prove that genetic anomalies cause some disease, it is harder to prove that genetic similarities are due to links in genealogy. (33)

Furthermore, it is unclear whether a person's genetic ancestral lineages are due to common geographical origins(33), an assumption that ethno-geographical analyses make. There is also the issue of accuracy and precision in ethnicity-based analyses. (33) Technological limitations in genealogical sequencing can establish the continental origins of an individual with relative precision, but fails to accurately distinguish between different ethnicities within a given continent. (23) This is partly because Western-American genetic research has disproportionately focused on people of European descent as the reference genome, such as the

case of 23andMe, which disproportionally focuses on Ashkenkazi Jews of Eastern Europe. (23) As a result, testing sensitivity is highly sensitive to the genetics of Ashkenkazi Jews while being unable to distinguish between sub-populations of non-European continents. (23) Yet, 23andMe advertises a precise ethnic breakdown of race genealogy by any country, a feat overexaggerated except for (Jewish) European ethnicities. In fine print, 23andMe warns it cannot detect the ancestry of people with mixed ethnicities (admixture), or determine which marker came from which parent, thereby compromising the ability of the test to report accurate genealogical data. (23)

Lastly, the contention of scientific validity is further reflected in the turbulent history of 23andMe and its regulatory battle with the United States' Food and Drug Administration (FDA). 23andMe was founded in 2006, and initially operated without public health regulation as a commercial service in California. (15) Only in 2009 did New York and California mandate 23andMe to obtain a Clinical Laboratory Improvement Amendments (CLIA) license to continue business. (15) Since 2008, the US FDA required the regulation of 23andMe tests as medical devices, with federal approval to market its service. (15) In 2013, the FDA sent a warning letter to 23andMe, as the company had not "analytically or clinically validated the personal genome service for its intended uses."(15) In other words, 23andMe's test results showed high variance in reproducibility on ancestral lineages, and the SNPs were claiming too much unproven health risks. As a result, 23andMe suspended its health-related genetic tests and scaled back its range of SNPs while undergoing regulatory review. (15)

Upon their subsequent efforts to follow FDA regulations, their services began to resume and in 2014, they expanded their services to Canada, Australia, and the United Kingdom. (15) However, the FDA was clear to establish that test results could only be marketed for genetic screening, not genetic diagnosis. (34) In other words, the tests cannot predict with scientific certainty an individual's risk of developing a disease or their ancestral background. The extent of genetic testing could only report specific variants within a person's genome, but not what the variants necessarily mean. Such a history of regulatory contention is not unique to 23andMe (6,7). Many DTC-GT companies face regulatory restrictions that are not publicly disclosed to consumers during the advertisement process. The question of regulatory harmonization also becomes an issue when companies operate in a different country (i.e.: USA) than what they market to (i.e. Canada), impacting the scope and quality of tests that a company can offer. Therefore, it is important for consumers to check the scope of DTC-GT regulation for their country, as it can affects how genetic data is used and interpreted.

The legal, epistemic and regulatory issues in data interpretation compromise the scientific validity of DTC-GT. These issues are not a problem in and of itself as long as consumers are aware of what the tests really measure. However, these issues become problematic due to ethical consequences that can arise as a result of undergoing DTC-GT. Consumers who do not understand the full extent of what these tests claim may mistakenly believe sweeping generalizations about their genetics or engage in detrimental behavior that they otherwise would not make without the test results. Without the guidance of a clinical genetic counsellor to interpret the data, the duty falls on the consumer to be wary of ethical complications. The next section provides a framework on common ethical issues arising from DTC-GT, so that consumers have the necessary tools to make their own decisions regarding health and ancestry genetics.

3.2 | Ethical considerations in direct-to-consumer genetic testing

This section will analyze broader contextual issues of DTC-GT from the ethical frameworks of social disability and feminist ethics. Although these frameworks are used to center the ethical discussion of DTC-GT, they are not exhaustive, and the same situation could be examined from other ethical frameworks (i.e. utilitarianism, liberalism, virtue ethics).

3.2.1 | Genetic health: geneticization, disability and harmful behaviors

One of the biggest ethical concerns which coincided with the development of genetic testing in the early 1990's was the idea of geneticization (35): the tendency to define differences between individuals as largely or entirely based on genetics. This definition in the context of genetic testing implies that there is some predictable correlation of genetics (the DNA sequence) to an observable phenotype. DTC-GT companies like 23andMe rely on this paradigm to advertise their services. This is evidenced by 23andMe's marketing of their genetic tests to reveal some 'essential' characteristic about a person's genome through a genetic "health predisposition" or "carrier status" test. (36) However, geneticization can lead to genetic discrimination, which is the partial and unfavourable treatment of individuals within social, political, or legal planes due to differences in their genome. Genetic discrimination is problematic, especially in the context of disease management, because decisions regarding the wellbeing of humans are made on the basis of a qualitative interpretation that a person's genome correlates to some physical or psychological state. (35) In reality, scientists and experts alike recognize this reductionist belief rests on shaky epistemic grounds; as we have seen, a person's genome may not necessarily be a direct cause of disease.

The ethical implications of geneticization go beyond what a DTC test result states. Today, geneticization and genetic discrimination can be embodied through health insurance practices for example. In Canada, Bill S-201 was passed in 2017 to prohibit the use of genetic test results to determine insurance claims below $250,000.‡(16-18) Though this law aims to prevent genetic discrimination, insurance companies can still ask and encourage individuals to disclose their DTC-GT results. (16) This law was made in an effort to combat specific practices of genetic discrimination, but it does not stop insurance companies from promoting the idea of geneticization as an ideology. Geneticization is the underlying belief that allows genetic discrimination to manifest in different ways. Barring one form of genetic discrimination does not prevent other forms to take place or develop as a replacement. Laws stand to regulate existing practices, not ideologies. (37) Therefore, consumers should be aware of the larger ethical consequences and 'what it means' to disclose their genetic information. Allowing insurance companies to obtain DTC-GT blurs the distinction between geneticization as a theoretical concept and genetic discrimination as a tangible practice.

Another consequence of geneticization is the tendency for DTC-GT to promote risky behaviour in the name of preventative healthcare. (8,38) Without the guidance of a genetic counsellor, consumers may engage in harmful actions that they would otherwise forego. Such is the case of buying black-market prescription drugs to pre-emptively 'cure' a disease, or undergoing surgery because test results revealed a variant of cancer. (8) In a study of 25 individuals who underwent 23andMe's testing service and tested positive for BRCA1/2 variants of breast cancer, 4 individuals underwent preventative surgery for the sake of risk reduction, before actually developing the cancer. (9) This contradicts the scientific evidence stating there is currently no effective genetic screening protocol that can reduce mortality from ovarian cancer for those who carry BRCA1/2 pathogenic variants. (10,39) In other words, 23andMe testing encouraged individuals to undergo potentially unnecessary surgical procedures . As mentioned, having a genetic variant does not guarantee the result of developing a disease, but undergoing surgery guarantees subjecting the individual to all associated surgical risks. (11,40) Most often, DTC-GT companies do not explicitly inform consumers of the risks of 'preventative healthcare', nor do they prevent consumers from engaging in harmful behaviours after the test. (41)

Lastly, social disability ethicists argue against the idea of geneticization, as they do not support the conceptualization of health on a genetic basis. (25) This is because there is an epistemic barrier between genetic conceptions and lived experiences of disease. (42) In other words, people do not 'know' what it's like to live with a genetic variant, but people know what it is like to feel

debilitated in health. Social disability ethicists would argue the debilitating experience is better embodied by social descriptions (43); health is shaped by a variety of elements, with genetic variation being only one element to consider. DTC-GT can also become a burden to health if it increases anxiety or promotes risky behaviour. (43,44) Instead, social disability ethicists believe whether an individual has a negative or positive outlook to their health largely depends on how society treats them and the access to accommodations that society provides. (25) Individuals should not need a genetic test to legitimize their embodiment of disease or make proactive decisions regarding their wellbeing. They can look to other aspects of healthcare (such as caregiver support, workplace accommodations, etc.) to address a variety of bodily standards and functions. (43) Social disability theory thus works to oppose the very ideology of geneticization, and argues that the idea of disease/disability is not due to a person's inherent (genetic) nature, but a product of societal barriers.

3.2.2 | Genetic ancestry: racial constructions, essentialism, and racism

The main ethical debate surrounding genetic ancestry tests is the distinction between race essentialism and socially constructed views of race.§ Race essentialism is the belief that race has a biologically distinct and quantifiable 'nature'. (2) In the context of DTC-GT, it means race can be defined by the specific composition of genetic haplogroups, leading to an individual being characterized as 40% Irish and 60% Native American, for example. However, it is important to understand that race essentialism developed as a consequence of the Human Genome Project and the genomic revolution in the 1990s (46), with ethical correlations to geneticization discussed earlier. Essentialism contrasts the idea that race is a social construction: a product of personal and social identities, contextually situated and dynamically evolving in time. (47) For example, an African or a Black American may have the same genetic composition of race, but their conceptualization of personal race would be different because of ethnic differences in cultural practices, beliefs and societal context.

The idea of race as a social construction has an ethical basis in feminist frameworks of relational autonomy, where our racial and ancestral identity is related to our conception of the 'self' as socially embedded agents in society. (47) The conception of the 'self' exists as a relational identity to intersecting social determinants, such as race and ethnicity, but also sex, gender, class, etc. (47) Thus, 'whiteness' is defined not only by a person's genetic race, but by the social privileges or disadvantages afforded to a particular identity of race within the greater set of cultural norms and practices in which they exist. (47) For feminist ethics, racial identity is not defined by a person's genetic links to outward appearance, but instead on social practices that shape how society treats individuals based on their outward appearance.

The ethical distinction between race essentialism and social construction rests on how we use these racial frameworks to justify social phenomena. Race essentialism becomes problematic when it leads to racism and discrimination on the basis of genetics. (4) This can be exemplified by using ancestral genetics to justify discriminatory health practices, such as the BiDil controversy which saw the FDA approve race-based drugs without a clear empirical link between race and biology. (48) It sensationalized race genetics for commercial and regulatory gain, for a Black community that already faces racial discrimination in other aspects of their lives. (48) This situation is analogous to what can happen in race-based approaches to health. A 23andMe study showed that people of Ashkenazi Jewish ancestry are genetically predisposed to BRCA1/2 mutations. (12) Should we consequently create a similar race-based solution to targeting breast cancer in Ashkenazi Jews, or promote further studies using this approach? Answering 'yes' presumes accepting the viewpoint of genetic essentialism, but could be challenged upon the observation that 23andMe's reference genome draws heavily on individuals with Ashkenazi Jewish ancestry. (23) It is expected that health risks will correlate with Ashkenazi Jewish ancestry when the reference genome is composed of *these* individuals. This issue of questionable science becomes an ethical issue when race-based prac-

tices are used to differentially treat certain populations over others.

Furthermore, racial essentialism can lead to identity politics issues of gatekeeping on the basis of genetics. (49) Someone of mixed American ancestry could be denied Native-American status on the basis of not having enough genetic Native ancestry, despite adopting Native cultural norms and practices in their life. (49) This form of genetic essentialism stems from the epistemic issue that Western-American DTC-GTs lack reference data for non-European races. (23) These examples highlight not only the epistemic limitations of race essentialism, but also the ways social constructions of race could be a better tool to inform our understanding of race. Essentially, race according to genetic essentialism shifts the focus away from real issues of race (like racism), while legitimizing racial discrimination on the basis of genetics.

The last ethical dimension in ancestry genetics looks at the relationship between race essentialist beliefs and extent of genetic knowledge. A randomized control trial investigating the influence of genetic ancestry tests on racial essentialism showed that:

> *"Essentialist beliefs significantly declined after testing among individuals with high genetic knowledge, but increased among those with the least genetic knowledge. … These results indicate that individuals' interpretations of genetic ancestry testing results, and the links between genes and race, may depend on their understanding of genetics" (13)*

How we understand race depends on how well we understand epistemic limitations in the genetic testing process. The more informed the individual is on the biases of the process, the less likely they will adopt racial essentialist beliefs. (13) This phenomenon is not a major ethical concern in clinical contexts of genetic testing, as genetic counsellors are present to interpret genetic data from an external perspective. However, DTC-GTs lack the epistemic diversity of genetic counselors. (13) In consolidating genetic screening + data interpretation into one unified process, consumers are exposed to the one (and often essentialist) view of race interpretation promoted by DTC-GT companies. (46) In this sense, there is a greater ethical duty for consumers to avoid essentialist-based beliefs by not taking the company's interpretation of race/ancestry genetics at face value. For this reason, greater caution must be taken before adopting race-based views of genomic analysis.

4 | CONCLUSION

So far, this report has listed the main ethical issues of health and ancestry DTC-GT, arising from epistemic issues related to the interpretation of genetic data. I have highlighted how the DTC-GT process frames individuals as consumers, and the regulatory consequences that comes with this distinction. I have also explained some epistemic issues behind the scientific process of the genetic testing process, and how a misinterpretation of genetic data can lead to ethical issues of geneticization and race essentialism.

Broadly speaking, there are further ethical considerations of DTC-GT not covered by this paper, such as:

- *Informed consent*: DTC-GT companies may not present to consumers a clear understanding of the testing, interpretation, and usage of information process. (4)
- *Data privacy*: the scope of privacy policies may not protect consumer genetic data from its usage of data in non-commercial purposes, especially when privacy/Terms of Use policies can be changed anytime by the companies that set them. (4)
- *Biobanking*: the storage of genomic data for pre- and post-commercial usage can complicate ownership and usage rights of genetic information. (50)
- *Further research*: questions of what is owed (monetary compensation or otherwise) may not be addressed when a company uses consumer data for internal/external research. (33)
- *Regulatory scope*: lack of regulatory harmonization

and third-party enforcement of DTC-GT companies means that all the ethical concerns above are subject to the (mis)management of the company itself. (4)

These issues extend beyond the scope of epistemic data interpretation, but nonetheless are important issues to take into account when choosing to undergo DTC-GT.

DTC-GT may seem like an attractive option because it is commonly marketed to individuals. Consumers should realize that DTC-GT is not the only way to be proactive about personal health. Alternatives to DTC-GT include:

- *Clinical sequencing with counselling*: the conventional path of working with genetic counsellors can alleviate epistemic issues regarding data interpretation, but ethical issues of geneticization/essentialism can still persist in lieu of a good counsellor. (51)
- *Epigenetic screening, RNA/protein assays*: these profiles reveal different molecular states not covered in DTC-GT sequencing, and challenges epistemic misconceptions about the sole causal agency of genetics to disease. (52)
- *Metagenomic sequencing*: a profile of commensal microbial entities can highlight its interaction with host systems in its native environment, further dispelling epistemic misconceptions about the 'essentialist' effect of host DNA. (53)

All these processes reveal some other aspect of a person's molecular composition and when done in combination, can paint a diverse molecular profile that moves away from a causal genomic view of molecular processes. However, each method also poses ethical concerns regarding genetic reductionism, and not all processes have been adapted for large-scale clinical application. (53)

There is no ideal method for understanding genetic health and race. Direct-to-consumer genetic tests offer consumers the ease and power of taking genetic data 'in their own hands', at the cost of compromising scientific validity and potentially exacerbating epistemic-driven ethical issues of geneticization and race essentialism. (53) Though the ethical issues were formulated in the context of 23andMe, it is important to realize that other DTC-GT companies face similar ethical complications. (53) The consequences of geneticization will always be an issue when a company markets its business on the essentialist basis of genetics.

This report does not take a position for or against the use of DTC-GT; rather, it aims to highlight key ethical issues not explicitly addressed when consumers undergo the DTC-GT process. Until further work is done to address the epistemic, regulatory and legal issues, ethical implications will continue to exist. The issues thus presented provide consumers with the knowledge to make their own decisions regarding DTC-GT. The decision to pursue DTC genetic testing comes down to a matter of weighing personal values and tradeoffs: privacy, power of knowledge, speed of testing, scientific/epistemic validity, harms/risks, and broader ethical consequences are all factors to take into consideration. Perhaps, the best avenue for understanding health and ancestry is to forgo the genetic approach altogether; social disability and feminist ethics would advocate for a more comprehensive social understanding of health and ancestry as opposed to striving for genetic legitimacy.

5 | NOTES

* It is advisable for consumers to gauge the exact legal scope of the specific DTC-GT company of interest, for their specific geographical location. Some small subset of DTC-GT may be considered diagnostic, depending on regulatory policies of their geographical location Any lack of legal information should be assumed recreational.

† SNPs are areas of the genome with the highest rate of variance (a single base pair mutation) at a specific locus, which is often correlated to some phenotype.

‡ Canadian insurance companies already use discrimination (by habit, occupation, age, weight, etc.) to determine eligibility and rates of coverage. The law prevents further discrimination on the basis of genetic test

results.

§ Definitions of race and ethnicity: “Race is usually associated with biology and linked with physical characteristics such as skin color or hair texture. Ethnicity is linked with cultural expression and identification.”(45) In the context of DTC-GT, ‘race’ refers to the former biological context.

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NARRATIVE REVIEW
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Exercise-Induced Pulmonary Hypertension: How to Define, Diagnose, and Treat At-Risk Patients

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ABSTRACT

Introduction: Pulmonary hypertension (PH) is a devastating disease that progresses rapidly, leading to high patient mortality. This condition is characterized by high blood pressure in the pulmonary vasculature and poor pulmonary perfusion, resulting in patient fatigue, dyspnea, and syncope—especially upon physical exertion. A sub-clinical form of PH is referred to as exercise induced pulmonary hypertension (EIPH), where patients display normal resting hemodynamic properties but abnormal pulmonary responses to exercise.

Discussion: Recent evidence suggests that early intervention and treatment of PH can improve patient outcomes. However, little clinical evidence exists to support effective treatments of EIPH. This lack is due in part to the removal of EIPH from official guidelines, such as the European Respiratory Society in 2008. EIPH was removed from clinical guidelines because of a lack of consensus on what constitutes EIPH and a lack of agreement on standardized testing procedures for diagnosing EIPH. Emerging evidence suggests that exercise testing following a standardized protocol of stress echocardiography or right heart catheterization may allow for better classification of EIPH. This review proposes that a mean pulmonary artery pressure/cardiac output slope > 3 mm Hg/L/min or mean pulmonary artery pressure > 30 mm Hg with a pulmonary vascular resistance > 3 Wood units is both a sensitive and specific enough threshold to diagnose EIPH and is sufficient to consider specific treatment options.

Conclusion: Providing evidence for a consensus on the definition of EIPH, along with a validated and standardized testing procedure, will hopefully foster the progression of research on EIPH and further the development of treatments to improve patient outcomes.

KEYWORDS

Pulmonary hypertension, Exercise-induced pulmonary hypertension, Cardiopulmonary exercise testing

1 | INTRODUCTION

Pulmonary hypertension (PH) is a relatively rare yet devastating disease that is estimated to affect 1% of the global population under 65 and 10% over the age of 65. (1) PH is a progressive disease that results in decreasing exercise intolerance, dyspnea, fatigue, altered hemodynamic and cardiopulmonary function, and low long-term survival rates. (2, 3) If left untreated, the average length of survival for patients is approximately three years from the time of diagnosis. This delay is of concern because the average time from patient-described onset of PH symptoms to diagnosis of the disease is approximately 4 years. (4) In recent years, the prognosis for PH patients has been improved by the advent of new and improved therapies like pulmonary vasodilators and diuretics; however, a diagnosis of PH in Canada still increases the 1-year standardized mortality ratio by 7.2-fold. (5) Recent studies suggest that interventions conducted at earlier stages, or even pre-clinical stages of PH, may result in increased longevity and quality of life for patients. (6, 7) Therefore, a need exists for improved diagnostic methods to identify and treat patients with PH early in the development of the disease.

PH is characterized by abnormal pulmonary hemodynamics and high pulmonary blood pressure. This increased pulmonary blood pressure can be the result of several different underlying pathologies; however, the increase is typically caused by an obstruction to flow downstream of the right ventricle, either in the pulmonary arteries or the aortic valve. (8) Recently, the definition of PH was updated to be a resting mean pulmonary arterial pressure (mPAP) of 20 mmHg with a pulmonary vascular resistance (PVR) of 3 Wood units. (9) This new definition replaces the previous arbitrary cut-off of a mPAP 25 mmHg to include two standard deviations above the mean mPAP of 14 mmHg in healthy people. However, many people who have otherwise normal resting hemodynamics, display dyspnea and fatigue during moderate to mild exercise. When investigating the source of this exertional intolerance, researchers discovered that many of these people in fact had severely elevated mPAP and/or PVR while exercising. When tracked, a large proportion of these patients were found to develop abnormal resting hemodynamics, especially when other comorbidities like heart failure, systemic sclerosis, or scleroderma are present. (10-13) This observation led many people to believe that an intermediate step exists between normal pulmonary pressure and overt PH, which is referred to as exercise induced pulmonary hypertension (EIPH). (7, 14-18).

Until 2008, EIPH had been included in the official European Society of Cardiology and European Respiratory Society guidelines for PH. EIPH was described as a mPAP exceeding 30 mmHg, a pulmonary artery systolic pressure (PASP) > 50 mmHg, or a pulmonary capillary wedge pressure (PCWP) < 20 mmHg during exercise. (8) However, in 2008, the official guidelines for pulmonary hypertension diagnosis and treatment removed EIPH as a subset of PH. (8) The old definition of EIPH was abandoned because of its failure to accurately and consistently differentiate healthy patients from those experiencing true EIPH. Failure to differentiate healthy individuals was especially true in patients with increased cardiac outputs (CO), as their mPAP values would often exceed the 30 mm Hg threshold established for EIPH. (19, 20) In one example, a study found that 26% of healthy patients displayed a mPAP > 30 mm Hg with exercise, especially as COs exceeded 10 L/min. (21) Another issue that resulted in the old definition being abandoned was disparity in the methodology and exertion metrics used to diagnose EIPH. (22) Some researchers proposed that stress echocardiography (SE) measurements during exercise were sufficient to diagnose EIPH, while others, including the Canadian Thoracic Society maintained that right heart catherization (RHC) was necessary for diagnosis. (11, 23) Additionally, the formulas used to attain pulmonary pressure and vascular resistance varied between groups, as well as the actual exercise parameters used (ie, cycle ergometry vs treadmill tests). Therefore, consistency and accuracy in measurements was a major concern that ultimately forced the definition to be abandoned.

More recently, new thresholds for defining EIPH have been put forth; these new thresholds are demonstrated to be more sensitive and specific for defining EIPH. The

improvement of diagnostic techniques and methodology has led to more consistent measurements of hemodynamic properties. The definitions that were recently suggested for EIPH are a mPAP to CO slope of > 3 mm Hg/L/min (24, 25) or a mPAP >30 mm Hg with total peripheral resistance > 3 Wood units during exercise. (21) Since EIPH is viewed as a potentially more treatable stage of PH it is crucial to develop a standard diagnostic approach with reliable threshold parameters to accurately diagnose EIPH. (17) This review will briefly describe the etiology of PH and focus on creating a definition for EIPH, illustrating the gold standards for diagnosis, and discussing relevant interventions for patients.

2 | ETIOLOGY OF PH

PH is a progressive disease of abnormal pulmonary hemodynamics and increased pulmonary circulation pressures. (14) Currently there are 5 different clinical classifications of PH (**Table 1**) with different subclassifications based upon the mechanisms of onset. (9) The two most common causes of increased pulmonary pressure are increased PVR and increased left atrial pressure (LAP) (13, 26) In many cases, the initial onset of PH is idiopathic, however, the progression of EIPH typically stems from changes in the pulmonary vasculature that induce inflammation, vasoconstriction, cell proliferation, and hypertrophy. The result is exacerbated pulmonary damage inducing strain and dysfunction of the right ventricle (RV). (27)

It is important to try to understand the underlying etiology of the condition as it can help guide the treatment approach and the success of the therapy. For conditions with a known etiology, the treatment is often adapted to address the underlying cause of the PH. For example PH due to left heart disease is often treated with a mechanical intervention such as surgery to repair the defect (i.e. a valve replacement for a valvular disease). (8) For other etiologies where a mechanical intervention is not obvious or relevant, the endothelin (ET), nitric oxide (NO), and prostacyclin (PC) dependent pathways are currently being utilized as therapeutic targets in Canada. (23) ET activates two different receptor subtypes (ETA and ETB) present on vascular smooth muscle cells (vSMC) and endothelial cells (EC) (ETB only). Activation of ET receptors on vSMCs induces vasoconstriction, cellular proliferation, and hypertrophy, while activation on ECs results in vasodilation. (28) In PH it is believed there is a shift increasing ET expression on vSMCS that results in the deleterious phenotype associated with PH; therefore, ET antagonists such as Ambrisentan have been employed with relative success. (23, 29, 30) NO is a potent vasodilator that also inhibits platelet aggregation and thrombosis. Under normal conditions, ECs continuously produce NO using nitric oxide synthase (NOS), causing relaxation of vSMCs and inhibition of cellular proliferation. (31, 32) In PH, levels of NOS are greatly reduced resulting in an increased vasoconstriction and cellular hypertrophy. (29) Prostacyclin (PC) is produced in ECs through prostacyclin synthase and acts as a potent vasodilator. (27) PC binds to prostaglandin receptors and induces relaxation of vSMCs. In PH PC levels are diminished, contributing to the phenotype of vasoconstriction and cellular hypertrophy observed in PH. (33) Since all three of these pathways contribute to rising PVR and increased pulmonary pressures, they have been investigated extensively and make up the bulk of therapeutic targets for patients suffering from PH. (8, 23)

3 | MEASURING EIPH AND COMMON TOOLS USED FOR DIAGNOSIS

A common complaint of patients with undiagnosed EIPH or PH is exertional fatigue/dyspnea. Therefore, SE is a common starting diagnostic procedure followed by chest x-rays, electrocardiograms (EKG), echocardiograms (ECG), chest CT or MRI scans, and blood tests to identify the underlying cause and rule out conditions other than PH. (14) As exertional dyspnea/fatigue is the most frequent presenting symptom, it is often useful to attempt diagnosis of EIPH or PH using cardiopulmonary exercise testing (CPX). (22) However, some con-

cerns have been raised about making patients with compromised cardiopulmonary systems complete exercise testing. Despite concerns, a comprehensive study involving over 4000 patients who underwent CPX while presenting with high risk cardiac diseases found an adverse event rate of only 0.16%. (34) Looking at the 194 patients with PH in the study, there were 0 adverse events after CPX in PH patients providing reasonable proof of the safety of CPX in PH patients. CPX usually includes monitoring ventilatory-perfusion parameters along with right and left heart functioning either through non-invasive ECG or invasive RHC. (16, 22) From these tools, values of CO, PVR, PCWP (which estimates left atrial pressure), right ventricle regurgitation velocity, mPAP, PASP, ventricular elasticity and wall thickness, right atrial pressure, peak VO2, lactic acidosis, CO2 output, oxygen saturation, and minute ventilation (VE/VCO2) can be generated and used to assess the presence and extent of the progression of disease.

4 | CHALLENGES IN DIAGNOSING IN EIPH

Many of the parameters used to diagnose EIPH are estimated from derivations of the following formula for mPAP, assuming an ohmic linear relationship between the parameters. (22)

$$mPAP = PVR * CO + LAP$$

The assumption being that any changes in PVR or CO will result in linear increases of mPAP, and that increases in LAP through backflow will increase mPAP in a 1:1 ratio. However, this does not consider the dynamic responses of the pulmonary vasculature in responses to changes in pressure. In normal healthy individuals, pressure increases are quickly met with pulmonary dilation to normalize flow. Therefore, past predictions of mPAP from this formula may be inaccurate. Herve and colleagues (21) demonstrated that this formula for PVR only provided a 48% sensitivity, unless the patient had a purely vascular etiology (implying limited distensibility of the vasculature leading to a more linear relation). A more comprehensive alternative formula has been proposed to take into account the distensibility of the venous system. (22, 35)

$$mPAP = \frac{(1 + \alpha LAP)^5 + (5\alpha Ro * Q)^{\frac{1}{5}} - 1}{\alpha}$$

Where Ro is the resting total pulmonary resistance, as defined by the ratio of mPAP/CO, Q is pulmonary blood flow and is the distensibility coefficient of the vasculature. The coefficient can be obtained by measuring the pulse pressure of a large artery, but is often assumed as 2% in most species. (22) This formula better represents the pressure flow relation shown in a compliant vasculature and could potentially lead to more accurate mPAP approximations.

Another issue that arises from the way values are commonly derived from functional tests is the calculation of CO. It is often cited in literature that CO can be approximated equivocally from thermodilution or direct Fick measurements. (36) However, previous CO measurements had only been validated in resting patients and Hsu and colleagues found that using thermodilution actually greatly overestimated the prevalence of EIPH in patients, with a 20% increase in false diagnoses. (37) As CO increased in patients, the separation in predicted Fick and thermodilution COs increased, with thermodilution underpredicting CO relative to Fick measurements. This is extremely concerning, given the importance of accurate CO measurements in predicting other important parameters for diagnosing EIPH, such as total pulmonary resistance and PVR. Therefore, it is possible that the prevalence of EIPH has been overreported in the literature where studies used thermodilution.

Currently, there is a consensus on what constitutes normal resting values for many of the parameters described above, (i.e. mPAP <20mmHg). However, the definitions for what constitutes normal hemodynamic parameters during exercise remain elusive. Especially since some of the techniques used to diagnose PH at rest have not been well validated for measurements of

the same parameters during exercise.

4.1 | Difficulty in consistent measurements

A major difficulty in diagnosing EIPH is making consistent measurements on patients during exercise. Performing invasive RHC or SE on an actively moving patient can be a difficult procedure. In addition, normalizing the workload between patients to establish a normal PAP is challenging. (16) Often a cycle ergometer is used with patients in an upright position, with work values ranging from 10-30 W; however, other methods have been used such as treadmills or supine leg press. (22) This can lead to disparity in results, since patient stance/posture can have substantial effects on intrathoracic pressure and concomitantly on pulmonary pressure. (17, 38) SE is often used as a diagnostic tool as it is readily available in most clinics and is a non-invasive measurement, but SE has not been well validated for use during exercise. (18) One issue with using SE during exercise is that predictions of right atrial pressure often rely on measurements of the distension of the inferior vena cava. However, it is known that exercise lowers venous compliance and therefore can reduce the accuracy of observations made by SE. (18, 39) However, performing SE after the patient has finished exercise runs the risk of missing important data, as hemodynamic parameters quickly return to resting levels within five minutes post-exercise. (40) Another issue with SE, is that PCWP, which is a standard measurement in the diagnosis of PH, cannot be calculated without direct invasive measurements such as RHC. Yet invasive measurements are not without their own problems, as they can be difficult to obtain during exercise because of large swings in intrathoracic pressure that accompany heavy breathing during exercise. (16)

4.2 | Variation in measurements of healthy individuals

One of the main reasons EIPH was removed from the official guidelines in 2008, and not reinstated in the updated guidelines released in 2019, was the lack of consensus among experts on what constitutes normal pulmonary pressures during exercise. Initially EIPH was defined as a mPAP>30 mmHg, but multiple studies have found that healthy individuals consistently exceed mPAP values of 30 mmHg during strenuous exercise, especially in well-trained athletes. (19-21) The caveat being that the increased mPAP and PASP seen with these individuals were accompanied by an increased CO, which fits in line with the observation that healthy individuals do not exceed a mPAP/CO slope of 3 mmHg/L/min. (19, 41) As well, studies have shown that 6% of otherwise healthy individuals over 50 have a PASP>40 mmHg as well as 5% of people with a BMI >30. (42) More recent studies have shown that healthy (non-athletes) cannot exceed PASP values of 40-45 mmHg at CO <20L/min during exercise. (41, 43) However, these studies excluded athletes.

PASP is most often estimated from the following formula:

$$PASP = 4V^2 + RAP$$

Where V is the maximum velocity of the tricuspid valve regurgitant jet and RAP is the right atrial pressure. Tricuspid valve regurgitation itself has been suggested as a defining criteria for EIPH as a regurgitant jet velocity of >3.0m/s, but in line with the findings that PASP can often exceed EIPH definitions, researchers found that athletes had an average peak tricuspid regurgitation velocity of 3.41m/s. (44) Therefore, the large variations of hemodynamic parameters in healthy individuals and trained athletes adds to the challenge of finding a single parameter to define EIPH.

4.3 | Predictive ability of Different Diagnostic Tools

The multifactorial nature of PH requires a large repertoire of diagnostic techniques to pinpoint the etiology of each patient's PH. Several methods that are effective in the initial screening of patients have proven to

be ineffective at diagnosing EIPH when used in isolation. Electrocardiograms, although useful for providing direction for further investigation, were shown to be inadequate at diagnosing PH with a sensitivity (true positive rate) of only 55% and a specificity (true negative rate) of 70%. (45) Minute ventilation (VE/VCO2) at ventilatory threshold and peak alveolar-arterial difference in PO2 were not sensitive enough to distinguish EIPH from normal. (18) The lack of standardized procedures for SE has led to both over and underestimations of PAP. (3) When compared to RHC, SE displays variable correlation values between 0.57-0.93 with PASP measurements (11) A more recent study found that 35 of 100 patients identified to have EIPH according to SE, actually had normal hemodynamics via RHC results. (15) Therefore caution must be used when interpreting SE results.

The current gold standard for diagnosing EIPH or PH is RHC. The biggest downfall of RHC is lack of availability and the inconvenience for the patient in using an invasive measurement. For this reason and also for simplicity, SE is often the preferred first method for screening patients of suspected EIPH or PH. (22, 23) Despite the limitations of SE, it allows for quick, easy and relatively reliable estimates, when conducted properly, of PASP, PVR, and pericardial effusions, as well as overall morphology of the heart and valves allowing for diagnoses of RV size and function, RA size, diastolic dysfunctions, valvular functions, patent foramen ovale, and intrapulmonary shunts. (45) However, the importance of standardized techniques used during SE to ensure more consistent and better interpretation of results cannot be understated.

5 | PROPOSED STANDARD PROTOCOL AND DEFINITION OF EIPH

Creating a definition for EIPH is challenging as it exists in an intermediary state between normal values and overt PH. Normal hemodynamic values used for diagnosis of PH have been shown to vary substantially even among healthy control patients during exercise, making it difficult to isolate clear standards for the subset of patients displaying EIPH. The traditional definition of EIPH being a mPAP >30 mmHg, PASP >50, or PCWP <20 mmHg during exercise, proved to be inefficient at adequately separating the distinct patient populations (healthy vs EIPH vs overt PH). Therefore, efforts have been made to revise and improve upon these thresholds to find parameters that are more sensitive and specific. It seems clear that a singular definition to define EIPH is not reasonable. Instead, a consensus between several parameters should be used for diagnosis. The best and most current thresholds for an EIPH diagnosis is: a mPAP > 30 mm Hg with CO < 10 L/min or a mPAP/CO slope > 3 mmHg/L/min; or a mPAP > 30 mmHg with a resistance greater than 3 Wood units (**Table 2**). These thresholds are shown to be 93% sensitive and 100% specific. (21, 24, 25) Several other parameters are useful for unlocking the etiology of EIPH, albeit insufficient for diagnosis. VE/VCO2 can be useful for separating stages of PH, as VE/VCO2, increases as PH worsens, but is unchanged in EIPH patients compared to normal. (46) Whereas PASP and PCWP can be used as indicators for the presence of heart disease (45) Barst and colleagues describe the ideal testing methodology in their review, from which we propose a standardized methodology to test for EIPH (**Figure 1**). (45)

6 | SHOULD WE TREAT EIPH

The lack of a current formally acknowledged definiton for EIPH does not mean the disease does not merit treatment. However, at the time of this review, a limited number of studies have been conducted to investigate the efficacy of treating patients with EIPH. This phenomenon is despite the fact that numerous studies have shown that the earlier the intervention, the better the prognosis for patients with PH. (8, 47-49) PH therapy has been shown to slow and prevent further disease progression as well as improve hemodynamic properties of the patients. (6) Kovacs et al (47) reported greater decrease in PAP and PVR with intervention earlier in the stages of disease progression (lower WHO functional class) . Ear-

1. Include patients with exercise intolerance whose resting mPAP <20 mmHg.
2. Dynamic exercise in supine position on a stress echocardiography bed, if possible, to allow for constant measurement with SE while patient pedals on a cycle ergometer.
3. Use estimated exercise capacity to design number of work steps and work increments to reach maximum tolerable workload within 10-15 minutes.
4. Take baseline measurements while patient is pedaling at a workload of 0 watts.
5. Increase workload increments at constant rate, between 10-30 W.
6. Constantly measure mPAP using peak pulmonary regurgitation Doppler signal.*
7. Take measurements of PCWP, PASP, and CO (through direct FICK measurement).
8. Stop procedure once the thresholds for EIPH have been met (mPAP/CO slope >3 mmHg/L/min or mPAP >30mmHg + TPR >3 WU, or patient reaches maximal tolerable workload.
9. If uncertainty in the results of SE proceed to RHC and repeat steps 2-8.

FIGURE 1 Proposed standardized protocol for exercise hemodynamic testing.

*For a comprehensive review on SE techniques, see reference (51).

lier treatment has also been suggested to lead to less disease morbidity. (48, 49) A recent study demonstrated that patients with EIPH (defined as a mPAP/CO slope > 3 mmHg/L/min during exercise) had a 2-fold increase in the hazard ratio of a future cardiovascular event or death comapred to patients with a normal mPAP/CO slope during exercise. (50) As EIPH is considered by many to be a distinct and early stage in the progression of PH, it stands to reason that early intervention will delay the progression into classically defined PH, extend the expected lifespan of patients, and greatly improve patients' future quality of life. Not only does early diagnosis lead to a better prognosis but also to more robust treatment options for the patients. Late stages of the disease often require continuous IV administration of drugs, which greatly diminishes patient quality of life. Whereas for earlier stages, patients often receive oral therapies which are less intrusive and more convenient.

Currently, no drugs are specifically tailored for treatment of EIPH; however, some clues can be taken from a study that looked at scleroderma patients displaying normal pulmonary hemodynamics but abnormal exercise hemodynamics at rest. Saggar et al (48) showed that invasive measurements were easily able to distinguish different stages of abnormal hemodynamic progression, and the authors suggested that early treatment of patients with EIPH-like symptoms using a pulmonary vasodilator (ambrisentan) may yield promising results. Many patients whose PH is derived from pulmonary vascular disorders are prescribed pulmonary vasodilators, and the results from these studies may yield some additional insight into EIPH treatment. The more recent therapy of choice for treatment of early stages of PH are endothelin blockers (ETA and ETB). One such drug currently on the market is bosentan, which has been shown to improve exercise capacity (increased Six-Minute Walk Test levels), vascular resistance, and cardiac index. (6) Bosentan was also shown to decrease brain natriuretic peptide levels which along with improved vascular resistance are predictive factors for survival. The most promising characteristic of endothelin blockers so far is the lack of reported adverse side-effects. The most common reported side-effect has been increased liver amminotransferase levels and has yet to be correlated with adverse events. (6) Other drug targets include prostanoids and phosphodiesterase-5 inhibitors. However, these therapies are less preferred for treatment of earlier stages of EIPH because they either have more adverse side-effects or call for less-convenient administration methods, like IV injections. (27)

In Canada, there are currently 10 PH-specific treatments that are approved and have signficiantly improved patient quality of life and long-term survival. (23) Despite the promising results of these therapies in treating many conditions, they have proved less effective in treating PH caused by systolic and/or diastolic dysfunctions. (49) Typically, anti-clotting agents, such as warfarin, and diuretic agents are prescribed to patients with resting PH; however, whether these treatments would be beneficial for patients suffering from EIPH is uncertain. (27) Calcium channel blockers may also be prescribed to PH patients, but these drugs' safety and effi-

cacy profiles may not warrant use in patients with EIPH. Finally, dual therapy has been shown to provide an additional advantage when compared to monotherapy, yet again, no evidence exists for efficacy of dual therapy in treating EIPH patients.

In general, very little data supports the efficacy of treating EIPH. Nevertheless, studies evaluating the effect of treating early stages of PH appear to be advantageous. With the fast progression of PH and high mortality rate associated with the disease, more studies evaluating the efficacy of EIPH treatment are necessary. As most cases of EIPH are believed to be the result of pulmonary vascular diseases or left heart disease (both of which increase PVR and pulmonary pressure), pulmonary vasodilators and ET antagonists would appear to be the most promising therapy for treating patients with EIPH. (22, 27) Consequently, further studies are needed to provide a conclusive argument for the efficacy of treating EIPH.

7 | CONCLUSION

EIPH has consistently been shown as a distinct entity that is intermediate between normal hemodynamics and overt pulmonary hypertension. However, the lack of consensus on defining criteria for EIPH and an absence of standardized treatment methodologies has led to the poor state of knowledge on treatment efficacy for this subset of patients. With evidence showing that treatment of the early stages of PH leads to increased longevity and better quality of life for patients, it is crucial to evaluate if these results are transferable to patients suffering from EIPH. This review proposes that a mPAP/CO slope > 3 mmHg/L/min or mPAP >30 mmHg + TPR > 3 Wood units is both a sensitive and specific enough threshold to diagnose EIPH and is sufficient to consider specific treatment options. Having a set EIPH definition for clinicians along with the standardized protocol provided here will allow research to move forward on treatments for EIPH, and hopefully lead to a better future prognosis for patients who develop pulmonary hypertension.

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1. PAH
1.1 Idiopathic PAH
1.2. Heritable PAH
1.3. Drug- and toxin-induced PAH
1.4. PAH associated with:
1.4.1. Connective tissue disease
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.5. PAH long-term responders to calcium channel blockers
1.6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7. Persistent PH of the newborn syndrome
2. PH due to left heart disease
2.1. PH due to heart failure with preserved LVEF
2.2. PH due to heart failure with reduced LVEF
2.3. Valvular heart disease
2.4. Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. PH due to lung diseases and/or hypoxia
3.1. Obstructive lung disease
3.2. Restrictive lung disease
3.3. Other lung disease with mixed restrictive/obstructive pattern
3.4. Hypoxia without lung disease
3.5. Developmental lung disorders
4. PH due to pulmonary artery obstructions
4.1. Chronic thromboembolic PH
4.2. Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
5.1. Hematological disorders
5.2. Systemic and metabolic disorders
5.3. Others
5.4. Complex congenital heart disease

LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. Reproduced from Simonneau et al. under Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0). (9)

TABLE 1 Updated clinical classification of pulmonary hypertension

Definition	*Characteristics*
Pulmonary hypertension	Resting mPAP 20 mmHg
	Resting PVR 3 Wood Units
Exercise Induced pulmonary hypertension	mPAP/CO slope > 3 mmHg/L/min during exercise
	mPAP > 30 mmHg with a PVR >3 Wood Units during exercise

TABLE 2 Proposed hemodynamic definitions of pulmonary hypertension and exercise induced pulmonary hypertension

NARRATIVE REVIEW
McGill Journal of Medicine

The Interplay Between COVID-19 and Cardiovascular Disease

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ABSTRACT

Introduction: The emergence of the global COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has created a substantial burden on healthcare systems worldwide resulting in over 4 million deaths. The systemic impacts of COVID-19 infection are severe and broad in their implications, and the cardiovascular system is no exception. The SARS-CoV-2 binds the angiotensin-converting enzyme-2 (ACE2) receptor to infect host cells, with ACE2 representing a critical regulator of blood pressure homeostasis and proper cardiovascular functioning.

Discussion: Patients with a history of cardiovascular disease are at an increased risk for hospitalization and mortality, and COVID-19 infection has now been demonstrated to initiate acute, but serious, episodes of cardiovascular events such as stroke or myocardial infarction (MI). As cases continue to rise around the world, understanding the interplay between COVID-19 infection and the cardiovascular system will be important for healthcare systems to adequately respond to the pandemic and prepare for future challenges.

Conclusion: Evidence suggests that COVID-19 infection can spur the onset of various cardiovascular pathologies, including thrombosis, stroke, arrhythmia, and MI, and these complications contribute to poorer patient outcomes. Patients presenting with symptoms of cardiovascular disease may also be foregoing medical treatment out of fear that is brought on by the pandemic or due to strain on healthcare systems preventing access to care. The direct physiological and indirect social consequences of COVID-19 will undoubtedly lead to further challenges for healthcare systems now and in the future.

Relevance: This paper discusses the deleterious cardiovascular consequences induced by the global COVID-19 pandemic.

KEYWORDS

COVID-19, Cardiovascular disease, Stroke, Myocardial infarction, Hypertension

1 | INTRODUCTION

In December of 2019, the world was introduced to a novel coronavirus, coined the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the Corona Virus Disease-19 (COVID-19) pandemic. Since its emergence in China, COVID-19 has escalated into a global pandemic infecting over 199 million people and resulting in over 4.2 million deaths worldwide. (1) As case counts continue to climb, it has become increasingly evident that patients with underlying cardiovascular disease have an increased risk of mortality and morbidity as a result of COVID-19 infection.

Cardiovascular disease encompasses a wide range of pathologies including heart disease and stroke and is reported by the World Health Organization as the leading cause of mortality worldwide. Clinical and epidemiological evidence presents a clear link between pre-existing cardiovascular disease and the severity of COVID-19 infection, as people with underlying cardiovascular disease appear to be more vulnerable to becoming severely ill and/or dying from the virus. (2) However, the association between infectious disease and cardiovascular disease is not a recent discovery. Over the last century clinicians have noted an increase in incidence of acute myocardial infarction (MI) during outbreaks of influenza. (3) In a cohort of 332 patients, the incidence of admissions for MI was six-times higher during the 7 days after confirmation of influenza infection than during the control interval (1 year pre-and post-confirmed influenza infection). (4) Other observational studies using clinical data have further confirmed an increased incidence ratio and increased odds for adverse cardiovascular reactions following lab-confirmed influenza infection in large cohorts of patients. (5, 6) While these studies give strong support for influenza's role in increasing the likelihood of cardiovascular events, the pathological mechanisms underlying these observations have been reconsidered in the wake of the global COVID-19 pandemic.

Considering the rapid spread of COVID-19 across the world and the inability of countries to address and adequately respond to the effects of the pandemic, there is an increased need for understanding the interplay between COVID-19 infection and cardiovascular disease. This review will briefly introduce how COVID-19 interacts with the cardiovascular system, describe why patients with cardiovascular disease are at an increased risk of succumbing to COVID-19, and discuss what the long-term cardiovascular implications of COVID-19 infection could mean.

2 | THE MECHANISMS BEHIND COVID-19 INFECTION AND RELEVANCE TO THE CARDIOVASCULAR SYSTEM

COVID-19 infection is described as having three phases, beginning with mild upper respiratory syndrome, followed by a parenchymal pulmonary phase characterized by marked hypoxemia, and finally progression to a hyperinflammatory prothrombotic phase with multiorgan dysfunction and strong potential for thromboembolism. The substantial proinflammatory response to viral infections upregulates the frequency of immune cell subsets, such as macrophages, that induce a cytokine storm. Further systemic effects include increased expression of tissue factor, markers of thrombin generation and platelet activation, complement activation, and an increased risk of intravascular thrombosis. Whether, and to what degree, the clinically recognized cardiovascular manifestations of COVID-19 are a direct result of viral injury, prolonged hypoxemia, vascular endothelial cell infection/inflammation, cardiac pericyte infection, or intravascular thrombosis remains unknown. Vascular complications of COVID-19 have also been reported with evidence of viral particles within vascular endothelial cells and diffuse vascular endothelial cell injury associated with increases in inflammatory mediators of the lungs, heart, kidneys, and intestinal tissues that could culminate in thrombotic disease, stroke, arrhythmias, myocardial infarction, neurological manifestations including encephalopathy, acute respiratory distress syndrome, proteinuria, acute kidney injury, septic shock, and multiple organ failure (Figure 1). (7)

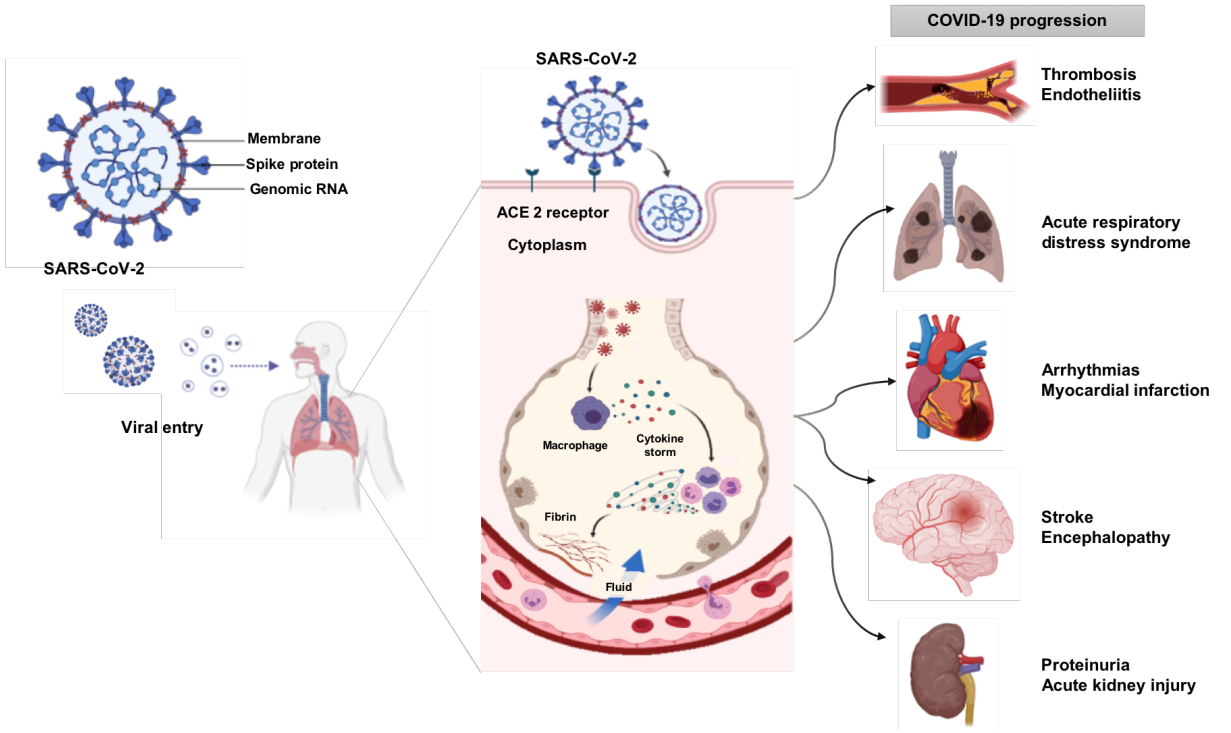

FIGURE 1 COVID-19 induces systemic inflammation that affects the lungs, heart, brain and kidney.

The coronavirus, SARS-CoV-2, that causes the disease, COVID-19, enters the cell using the ACE2 receptor. The principal point of entry is the upper respiratory tract. Viral entry into the cell induces inflammation in the respiratory tract, manifesting in progressive systemic inflammation with a cytokine storm. The increase of immune cells, cytokines, and inflammatory mediators affects several organs such as the heart, lung, brain and kidney. The progression of systemic inflammation can promote acute respiratory distress syndrome, acute kidney injury, thrombosis, stroke, arrhythmias, myocardial infarction, septic shock, and multiple organ failure.

Similar to the SARS-CoV-1 virus responsible for the 2002-2004 SARS epidemic, viral entry of SARS-CoV-2 occurs after proteolytic cleavage of the viral spike (S) protein upon binding to angiotensin-converting enzyme-2 (ACE2) receptor. This binding, in concert with S-protein priming by the host cell transmembrane protease serine 2 precursor (TMPRSS2), leads to host cell entry of the virus. Notably, SARS-CoV-2 is more pathogenic, at least in part due to its 10- to 20-fold increased binding affinity to ACE2 as compared to the SARS-CoV-1 virus (Figure 1). (8)The fact that SARS-CoV-2 utilizes ACE2 to gain entry into host cells provides strong evidence that COVID-19 infection can have a direct impact on the cardiovascular system. ACE2 is a key modulator of the renin-angiotensin-aldosterone-system (RAAS). The RAAS is a principal regulator of blood volume and blood pressure homeostasis; consequently, perturbations to RAAS signaling are at the root of many cardiovascular diseases like hypertension and heart failure. (9) ACE2 is positioned at a key intercept in this homeostatic process by virtue of being highly expressed in type II alveolar cells of the lung, cardiac myocytes, cardiac pericytes, and vascular endothelium, serving to convert the pro-hypertensive and pro-inflammatory peptide angiotensin (Ang) II to Ang 1–7. The effects of Ang 1-7 are multi-factorial and include vasodilatory, natriuretic, anti-inflammatory, and antioxidant effects. (10)

ACE2 expression levels are found to be increased in many cardiovascular diseases, possibly as a negative feedback mechanism to counter the effects of Ang II, and may help explain why the symptoms of COVID-19 appear to be more severe in patients with existing cardiovascular conditions. (11) Increased expression of

ACE2 provides more potential docking sites for SARS-CoV-2 increasing the risk for initial infection. Subsequently, when the virus gains entry to the cell, ACE2 is internalized and thus no longer able to exert its anti-inflammatory effects. (12) Viral particles have been identified in endothelial cells providing a possible trigger for endothelial damage throughout the cardiovascular system. (13) Endothelial damage is linked with hypercoagulability and may explain the increased incidence of thrombosis and ischemic stroke seen with COVID-19 infection. (14, 15) Infection of kidney endothelial cells is speculated to contribute to acute kidney injury in patients with COVID-19 and may exacerbate pre-existing cardiovascular conditions. (15, 16)

3 | DISCUSSION

3.1 | Deleterious Cardiovascular Manifestations of COVID-19 Infection

A concerning feature of COVID-19 is its unknown potential for long-term negative impact on cardiovascular health. A study released from Hong Kong demonstrated that 42.3% of COVID-19 survivors with non-severe disease and without overt cardiac manifestations displayed cardiac abnormalities up to four weeks post hospital discharge, with up to 8% displaying signs of myocardial injury. (17) The study was limited in patient number and in duration (only 4 weeks post infection); however, it raises concern for a potential future influx of patients with cardiovascular disease as the number of people who have been infected continues to rise. The substantial systemic inflammation induced by COVID-19 infection is likely to have a sizable impact on cardiovascular function, as the immune system is a known driver of many cardiovascular pathologies. The following sections will briefly describe what the most frequently reported cardiac manifestations of COVID-19 infection are and highlight the mechanisms for how COVID-19 could induce these poor cardiovascular outcomes.

3.1.1 | Thrombotic Disorders

It is now well established that COVID-19 infection can induce a hypercoagulable state that can leave those infected at an increased risk of acute thrombotic events or coagulation abnormalities. (14) In fact, thrombotic events were reported by one study in up to 31% of the patients admitted to the ICU with a diagnosis of COVID-19. (18) The occurrence of thrombotic events in COVID-19 patients is often identified by elevated circulating D-dimer levels(19), which is a fibrin degradation product. (20) In COVID-19 patients, the degree of D-dimer elevation correlates strongly with mortality(19, 21) and may serve as an important prognostic tool for monitoring the severity of the infection. Temporal increases in D-dimer levels are a strong predictor for patient mortality, resulting in a critical diagnostic tool for early intensive medical interventions. (21, 22) Other biomarkers used to identify the occurrence of thrombosis include Von Willebrand Factor, fibrinogen, and P-selectin, all of which have consistently been found to be elevated in COVID-19, marking the progression of the disease. (23)

Several mechanisms have been proposed to explain how SARS-CoV-2 induces this hypercoagulable state, including endothelial injury(24) and increased inflammatory, and prothrombotic factors. (22, 25) Pro-inflammatory cytokines such as interleukin (IL)-6, IL-1, and interferon- have been reported to be significantly elevated in COVID-19 patients. (25) These cytokines are known to damage endothelial cells, and this endothelial injury can trigger pro-thrombotic cellular cascades. Endothelial cells also highly express ACE2; therefore, they are more susceptible to infection with SARS-CoV-2. (13) Once infected, endothelial cells can enter in an inflammatory state of cellular death, termed pyroptosis, triggering further immune activation, inflammation, and subsequent thrombosis. Because the occurrence of thrombotic events in COVID-19 patients has been associated with poorer patient outcomes,(26) several clinical trials have emerged to identify the efficacy of anticoagulant therapies in the treatment of COVID-19 patients. (reviewed by (27))

3.1.2 | Stroke

In April 2020, it was estimated that as many as 4.9% of patients with COVID-19 had an episode of acute ischemic stroke during initial hospitalization. (28) As more data has been collected, it appears that stroke actually occurs in closer to 1-2.7% of COVID-19 patients. (29-32) However, whether SARS-CoV-2 infection contributes to the development of stroke is still controversial. A study of 14,483 patients infected with COVID-19 found a stroke prevalence of 1.1%, of which 42.6% were of cryptogenic in etiology. (32) The authors, along with several other groups, suggest that the hypercoagulability state associated with elevated D-dimer could be an underlying cause for the increased proportion of cryptogenic stroke in patients; consequently, COVID-19 could represent a novel stroke mechanism. (32-34) However, a more recent study looking at a database of 27,676 patients, 8 163 of which had confirmed COVID-19, found that acute stroke occurred in only 1.3% of infected patients, compared to 1% without COVID-19. This implies that COVID-19 did not significantly influence the occurrence of acute stroke. (31) Similarly, a smaller study from Italy did not find an association between COVID-19 infection and stroke incidence. (35) Notably, neither of the aforementioned studies investigated the incidence of cryptogenic stroke. Therefore, we cannot exclude the possibility that COVID-19 could influence the incidence of cryptogenic stroke. Further investigation is required to determine whether COVID-19 infection influences stroke occurrence.

3.1.3 | Arrhythmias

Arrhythmias, or alterations to the rhythm of the heart, have been one of the most common pathological cardiac manifestation of COVID-19 infection. A global study consisting of 4,526 patients from 12 countries and 4 continents found that approximately 18% of COVID-19 patients developed some form of arrythmia. (36) Even more concerning, the authors found that 40% of patients with arrhythmia needed to be mechanically ventilated, and only half survived. Another recent publication from Hong Kong followed patients with uncomplicated COVID-19 infection for up to 4 weeks post hospital discharge and found that 28% of patients developed an arrhythmia. (17) The mechanistic details for how SARS-CoV-2 can induce arrhythmia is still being deciphered, but there is emerging evidence that SARS-CoV-2 can directly infect cardiomyocytes and induce acute myocarditis, which can lead to the development of arrhythmias. (37, 38)

Interestingly, a 100-day observational study of 5,963 patients in the United States found that the incidence of ventricular arrhythmias decreased as the pandemic progressed, with the largest percent decrease in the states also with the highest COVID-19 case counts (up to 39% decrease in incidence). (39) In a subpopulation of 2,458 patients that had been monitored before the onset of the pandemic as well as during the pandemic, there was a significant reduction in ventricular arrhythmias. The authors speculated that this decline in the frequency of arrhythmia was due to a reduction in factors that favour or trigger arrhythmia, including reduced workplace and/or social stressors while working from home as well as decreased physical stressors induced by vigorous exercise. However, the authors remain uncertain about the exact reasons for the decreased incidence of arrythmia. It appears that COVID-19 infection can trigger the development of arrhythmia in infected individuals, but the social and workplace changes set in place for the pandemic may actually be decreasing the overall occurrence of arrhythmia in the general population. It will be interesting to follow future studies on the issue to see how the incidence of arrhythmias change as the pandemic progresses and safety protocols are lifted across the globe.

3.1.4 | Myocardial Infarction

In early 2020 the cardiovascular complications associated with COVID-19 became much more apparent, and studies finding an increased risk for MI associated with COVID-19 infection began to appear in the literature. (40) A study of 5,119 Danish COVID-19 patients found that the instance of acute MI was approximately 5 times

higher in the 14 days following COVID-19 diagnosis when compared to the 180 days before COVID-19 diagnosis. (41) A study across 4 hospital sites in New York City also found significant increases in the hazard ratio for arterial thrombotic events in COVID-19 patients, with MI being included under the umbrella of these events. (26) When looking at patients 45 years or older, the overall hazard ratio for arterial thrombotic events ranged from 1.65 to 2.71 with the highest hazard ratio associated with the oldest cohort (75 years old and up). In Sweden, a study investigating 1,946 cases of out-of-hospital cardiac arrest (OHCA) and 1,080 cases of in-hospital cardiac arrest (IHCA), found that 10% of all OHCA and 16% of all IHCA patients had COVID-19. (42) Patients with a confirmed COVID-19 diagnosis had a 3.4-fold (OHCA) and 2.3-fold (IHCA) increased risk of 30 day mortality in comparison to non-COVID-19 infected individuals.

In contrast to the information presented above, many hospital sites have actually seen a lower instance of MI than what would have be observed before the COVID-19 pandemic. In Italy, researchers found a significant reduction in admissions for MI across the country when they compared the week of March 12 to 19 in 2020 with that of 2019. (43) Surprisingly, a reduction of nearly 50% in MI admissions was observed from 2019 to 2020. A similar study looking at patients admitted for MI in Austria found that over the course of March 2 to 29, 2020, there was a nearly 40% decline in hospital admissions and in medical interventions for acute coronary syndrome and MI. (44) This may sound like a sliver of positivity in the midst of the pandemic; however, investigations into excess deaths due to COVID-19 paint a more sombre picture.

While the available literature presents a surplus of theory and speculation about hypothesized increases in the instance of MI with COVID-19 infection, there is relatively limited clinical evidence for increased MI in patients with a confirmed COVID-19 diagnosis. In theory, both type 1 and/or type 2 MI could be precipitated by COVID-19 infection. Type 1 MI is generally characterized by plaque rupture and thrombus formation(45), and type 1 MI could be induced by systemic inflammatory stress as a result of COVID-19, leading to plaque instability and rupture. (46) In the case of type 2 MI, hypoxic respiratory failure along with fever, tachycardia, and endocrine dysfunction, as a result of infection, may lead to an imbalance between cardiac oxygen supply and demand. (47) Both of these outcomes have a relatively poor prognosis without immediate medical intervention, and as more clinical data becomes available, it will be possible to better understand the cardiovascular risks associated with COVID-19. At the moment, our understanding of the real-world association between MI and COVID-19 infection remains limited to the data that has been released.

3.2 | Cardiovascular Disease and the Link with COVID-19 Mortality

Cardiovascular disease is one of the most frequently associated co-morbidities of COVID-19 infection, and it has been linked with a significant increase in the risk for mortality. (48) A summary of studies around the world that present data pertaining to the incidence of cardiovascular disease and COVID-19 mortality is presented in Table 1. In general, it appears that patients with cardiovascular disease who become infected are more likely to end up in the intensive care unit (ICU), and they are also at an increased risk for mortality, regardless of their country of residence. A global study found that the proportion of the population with cardiovascular disease significantly correlated with that same country's COVID-19 case fatality rate. (49) It was found that for every 1% increase in a country's incidence of cardiovascular disease, the death rate from COVID-19 was 19% higher.

The most prevalent comorbidity with COVID-19 upon hospital admission is hypertension (30-55% of COVID-19 patients, Table 1). The presence of elevated systolic blood pressure upon hospital admission was a strong predictor for the severity of respiratory distress and overall patient mortality. (50) Early in the pandemic, there was controversy as to whether or not the usage of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) should be discontinued in patients with COVID-19, as there

Prevalence comorbid CVD upon admission										
Country	Total Number of Patients	**Hypertension**	**Other CVD (%)**	**Intensive Care (% of those with HTN)**	**Intensive Care (% of those with CVD)**	**Intensive Care (% Total population)**	**Mortality (% of those with HTN)**	**Mortality (% of those with CVD)**	**Mortality (% of total)**	**Reference**
Worldwide	4526	2499 (55.2)	827* (18.3)	N/A	358 (43.4)*	N/A	N/A	403 (48.7)*	1420 (31.4)	(36)
Australia	103	37 (36)	16 (16)	11 (29.7)	6 (37.5)	18 (17.5)	4 (10.8)	3 (18.8)	4 (3.9)	(63)
Canada	811	361 (44.5)	171 (21.1)	149 (41.3)	67 (39.2)	328 (40.4)	97 (26.9)	N/A	166 (20.5)	(64)
China	1099	165 (15)	42 (3.8)†	24 (14.5)‡	10 (23.8)†, ‡	55 (5.0)	N/A	N/A	15 (1.4)	(65)
China	157	88 (56.0)	25 (16.0)§	N/A	N/A	N/A	22 (25.0)	12 (48.0) §	37 (23.6)	(50)
China	191	58 (30)	15 (8)	N/A	N/A	N/A	26 (44.8)	13 (86.7)	54 (28.3)	(22)
Italy	1591	509 (32.0)	223 (14.0)	504 (100) ‖	732 (100) ‖	1591 (100) ‖	195 (38.7)	N/A	405 (25.5)¶	(66)
Netherlands	952	374 (39.3)	184 (19.3)	195 (52.1)**	95 (51.6) **	476 (50.0) **	N/A	N/A	239 (25.1)	(67)
Spain	2070	919 (44.6)	324 (15.8)	N/A	N/A	N/A	255 (27.7)	102 (31.5)	393 (19.0)	(68)
USA	5700	3026 (53.1)	966 (35.8) ††	N/A	228 (16.7)	373 (6.5)	384 (12.7)	(N/A)	291 (9.7)	(51)
USA	393	197 (50.1)	82 (20.9) ‡‡	70 (35.5)	31 (37.8)	130 (33.1)	(N/A)	(N/A)	40 (10.1)	(69)
USA	586	353 (60.2)	215 (36.7)	N/A	N/A	196 (33.4)	60 (17.0)	105 (27.9) §§	82 (14.0)	(48)

TABLE 1 Prevalence of comorbid cardiovascular disease upon admission and its effect on mortality.

CVD – Cardiovascular Disease, Other CVD defined as coronary artery disease, heart failure, stroke, vascular disease, congestive heart failure or arrhythmia.

*Prevalence with an arrhythmia

† Prevalence of coronary heart disease and cerebrovascular disease combined.

‡ Numbers represent prevalence of composite endpoints: admission to intensive care unit, mechanical ventilation or death.

§ Based off of number of patients with arrythmia and cerebrovascular disease combined.

|| All patients in the study were admitted to the ICU. ||

¶ 920 patients were still hospitalized at the time of publication, therefore only the total number of patients that were either discharged or who had died were used for calculating %.

**Patients categorized as severely ill.

†† Prevalence of coronary artery disease and congestive heart failure combined.

was fear over the effects these commonly prescribed anti-hypertensives could have on ACE2 expression, and in turn, COVID-19 infection rates. (12) However, several studies have since emerged assuaging this concern, reporting no significant differences in hospitalization, length of stay, or mortality when these medications were administered. (48, 51-53) Interestingly, a recent observational study found that the transmission rate of COVID-19 to household contacts was actually lower in patients being treated with ACEI or ARB; however, caution must be observed in assuming a causal relationship. (54) Currently, the American Heart Association supports the continued use of RAAS inhibitors for the management of blood pressure in patients infected with SARS-CoV-2. (55)

3.3 | COVID-19 and Ramifications for Cardiovascular Disease Patient Care

Beyond the numbers of lives lost that were directly attributed to COVID-19 infection, there remains a potential for cataclysm in the backlog of patients from an over-

strained health care system. During the first and second waves of the COVID-19 pandemic in Canada, many hospitals forewent non-urgent procedures to reduce the burden on an already overstrained health care system. A study conducted in Ontario, Canada, showed that more than 1,200 medical procedures, including coronary artery bypass graft, angioplasty, and valve surgery, were postponed every month due to the pandemic. (49) This study revealed the serious disruption to essential health care services that were needed by patients living with cardiovascular disease.

In addition to decreased access to crucial medical services for patients, there may also be hesitancy on the part of patients to seek out medical attention due to social distancing and/or concerns of contracting COVID-19 in the hospital setting. (56) Consequently, it seems that many patients are not presenting themselves to health centres when experiencing mild symptoms of cardiovascular trouble out of anxiety or fear. (57) This phenomenon is ultimately leading to more deaths outside of the clinical setting and contributing to excess deaths not directly attributed to COVID-19. While hospitalization rates for MI have decreased in the United States and Europe, fatality rates for patients hospitalized for acute MI have increased. (58) This could be the result of patients who are experiencing mild symptoms avoiding medical care, while patients with severe symptoms seek out treatment. In turn, only the more severe cases would be treated in the clinical setting, and these patients are less likely to survive, increasing fatality rates. In addition, the patients experiencing mild symptoms may develop more severe symptoms later, leading to a poorer prognosis when they eventually present to the clinic. Speculation exists that the rates of hospital admissions for cardiovascular events will have a sharp increase over the coming months and years, as the patients who previously ignored their symptoms will be forced to access the treatment they initially avoided. This phenomenon is separate from the potential long-term cardiovascular complications that may arise from COVID-19 itself. (59) Taking into account (i) the increase in sedentary lifestyle as a result of large-scale lockdowns, (ii) the decrease in hospital visits for non-life threatening conditions due to disruptions in treatment from COVID-19, and (iii) the drug shortages paired with a lack of financial stability leading to fewer prescription refills, the occurrence of severe cardiovascular events has the potential to see a dramatic rise over the coming years. (60-62)

4 | CONCLUSION

The COVID-19 pandemic has had a devastating toll on health care systems worldwide. Patients with underlying cardiovascular disease are at an increased risk for hospitalization, admission to the ICU, and mortality when compared to the general population. In addition, accumulating evidence suggests that COVID-19 infection itself can induce the onset of various cardiovascular manifestations, including thrombosis, stroke, arrhythmia, and MI. It is clear that these complications contribute to worse outcomes for patients suffering from COVID-19. Finally, patients with overt cardiovascular complications may be foregoing medical interventions out of fear or anxiety elicited from the COVID-19 pandemic. Taken together, the COVID-19 pandemic has direct and indirect effects on the occurrence and management of cardiovascular disease, and it is a matter to be taken seriously by both clinicians and the research community alike.

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NARRATIVE REVIEW
McGill Journal of Medicine

Implication of COVID-19 on Post-Secondary Students' Mental Health: A Review

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ABSTRACT

Introduction: Nearing two nears into the current pandemic, COVID-19 is recognized worldwide for its devastating physical effects, with mandatory restrictions implemented to prevent the transmission of SARS-CoV-2. However, the world is only beginning to understand the pandemic's mental and social side effects. As such, current research on consequential mental health from COVID-19 is still novel, and there is much more to be learned concerning the long-term psychological effects and damage from the pandemic.

Discussion: The combination of online learning and social isolation due to COVID-19 has affected post-secondary students across North America as it relates to their overall well-being and mental health. Researchers have aimed to examine the psychological impact on students' mental health, primarily through cross-sectional studies and self-reported surveys.

Conclusion: Studies have determined that COVID-19 has increased mental health symptoms such as depression, anxiety, PTSD, as well as increased feelings of isolation, loneliness, and fatigue. Furthermore, drinking and substance use, poor sleeping patterns, and screen time have risen as a result of the ongoing pandemic.

Relevance: These findings call for post-secondary institutions, health care providers, and governments to prioritize the mental health of future generations while providing support and intervention programs. Future research should focus on further investigating COVID-19's long-term effects on the mental health of post-secondary students and exploring prevention methods.

KEYWORDS
COVID-19, Mental health, Quarantine, Universities, Students

1 | INTRODUCTION

The ongoing COVID-19 global pandemic has given rise to a new norm of societal living, consisting of a lifestyle predominately based on working, studying, and living from home. Governmental restrictions such as quarantine, lockdown, and curfew have forced individuals to stay home in an effort to prevent the spread of SARS-CoV-2. Globally, the public has adapted to the physical effects of the virus by wearing masks, practicing social distancing, and performing handwashing/sanitization. However, society has greatly overlooked the mental

and social effects of COVID-19. To date, researchers have conducted minimal in-depth studies on individuals' mental health as a side effect of the COVID-19 pandemic. In particular, the young adult population has been obligated to transform their learning and living methods over the past year. As a result, the well-being and mental health of higher education students have been severely compromised. In recent months, numerous studies of the pandemic's psychological impact on university and college students have been undertaken. Thus far, the research reveals that the COVID-19 public health crisis has greatly heightened mental health risk factors, including social isolation, unemployment, insecurity, and instability. (1) Also, feelings such as loss of freedom, separation from loved ones, uncertainty, and boredom have significantly contributed to the decline in youth mental health. (2) Furthermore, some studies show increased stress, anxiety, and depression symptoms in post-secondary participants. (1) Despite the newly found research regarding the declining mental health of higher education students due to COVID-19, much work remains to be done. Particularly, preventing stigmatization, raising awareness, and determining the pandemic's long-term effects on students are of utmost importance. In this review, topics including but not limited to motivation loss, isolation, depression, anxiety, drinking, substance use, screen time, sleep patterns, self-harm, and suicide will be addressed in the context of post-secondary students' mental health during COVID-19. The findings from this review will help to motivate future research on COVID-19's long-term mental and social impacts and encourage institutional action by higher education leaders to preserve the well-being of students.

2 | METHODS

This review conducted database searches on youth mental health during COVID-19, through Google Scholar, PubMed, QJM, and APA PsycInfo. Inclusion criteria included North American studies conducted between January 2020 - July 2021 that were published in English. Additionally, equal emphasis was placed on peer-reviewed articles, psychiatry research, and credible news articles that were relevant to student mental health. Exclusion criteria included studies conducted prior to COVID-19, with an exception being studies comparing the state of mental health before and during the pandemic. The databases were searched using variations of the following terms (and their synonyms): "COVID-19" OR "coronavirus" OR "pandemic" / "young adult" OR "adolescent" OR "youth" OR "teenager" / "student" OR "post-secondary" OR "university" OR "college" / "lockdown" OR "quarantine" OR "curfew" / "mental health" OR "psychological impact" / "social isolation" OR "loneliness" / "depression" OR "anxiety" OR "PTSD" OR "stress" / "North America" OR "Canada" OR "U.S." Results included a combination of peer-reviewed journals and abstracts. More than 100 studies were surveyed, with the final review limited to 12 studies highlighting the in-depth findings of student mental health during the pandemic. The final review included 31 publications, of which 12 were peer-reviewed journals, 5 were psychiatry research pieces, 5 were university published articles, 5 were relevant statistical sources, and 4 were important opinion news articles.

3 | DISCUSSION

3.1 | A World of Change

The start of the pandemic uprooted post-secondary students across North America from their socially fulfilling school environments, and the vast majority were sent home to finish their semester using an entirely new platform: Zoom. (3) On top of the uncertainty surrounding the rising spread of COVID-19, students were expected to make a major transition in terms of how they learned and managed routine daily tasks. Carlos Fuentes, a journalist for The Beacon Newspaper at the University of Portland, writes, "Zoom class backgrounds have become a collage of different houses, varying time zones and a range of outside stressors that go unseen on camera." (3) The years 2020-2021 will be remembered in history not only for a global pandemic, but also for other over-

whelming societal and environmental issues that were brought to the forefront, including climate disasters, systemic racism, and a tumultuous state of political affairs in the U.S. During an extended period of isolation, in addition to profound social, political, and economic unrest, recent studies have recognized young adults as the most vulnerable group for depression and anxiety during the pandemic. (4) Moreover, mental health professionals are becoming "increasingly alarmed about the deteriorating mental state of young people, who they say have been among the most badly affected by a world with a foreshortened sense of the future" due to the COVID-19 pandemic. (5)

3.2 | Fatigue and Loss of Motivation

Online learning and its unforeseen consequences were not an easy adjustment for most higher-level education students, in turn producing a loss of motivation and inspiration while increasing overall fatigue. (3) Studies show that in-person school environments are crucial for promoting academic motivation and social development. (6) As a Huffington Post article from February 2021 details, "From a spotty Wi-Fi connection, to broken links, a distracting work environment and poor communication from professors — virtual education comes with a major learning curve." (7) Audio delays and low-resolution calls require extended attention. (8,9) Without the support and engagement of in-person learning, students struggle to make it through their online classes and become susceptible to 'Zoom Fatigue.' (8,9) For most students, video calls expend more energy and require more focus than face-to-face interactions as non-verbal cues, tone/pitch of voice, and body language are more challenging to process online. (9,10) "Our minds are together when our bodies feel we're not. That dissonance, which causes people to have conflicting feelings, is exhausting. You cannot relax into the conversation naturally," says Gianpiero Petriglieri, an associate professor at Insead University. (10)

3.3 | Isolation and Loneliness

Moreover, the sudden transition to online learning triggered a strong sense of disconnect for students across North America. The support systems of university and college students largely vanished beginning in the spring of 2020 on account of COVID-19's isolation requirements. (4) A question posed by many schools and universities was how to "nurture social connection in the virtual, inherently disconnected environment of the pandemic?" (4) Students often experience feelings of loneliness and isolation without their friends for extended periods; therefore, friends serve as mental health protective factors. (3) The University of Oxford conducted a virtual longitudinal study, titled Achieving Resilience During COVID-19 (ARC), with findings highlighting that young people are lonelier in lockdown than their parents. (11) Likewise, in a self-response survey of 2,500 U.S. college students, 80% of participants said they would be more educationally successful if living with friends rather than at home. (3) As a Tulane University paper on loneliness and isolation in COVID-19 states, "Social support plays a key role in well-being, yet one of the major preventative efforts for reducing the spread of COVID-19 involves social distancing." (12) Even though social support is a known coping mechanism in times of crisis, its benefits are limited during the pandemic due to social distancing and other governmental restrictions implemented. (12) Additionally, "isolation has also disrupted the usual teenage transition, when young people move from belonging to their family to belonging to their peers," Dr. Vermeiren, a psychiatrist at Leiden University Medical Center, explains. (5) This developmental concern causes feelings of emptiness and loneliness, consequently leading students into a state of despair. (5)

3.4 | Depression, Anxiety, and PTSD

Faced with numerous restrictions, uncertainty, and a roller coaster of emotions, university and college students' mental health has declined, as evidenced by increased rates of depression, anxiety, and PTSD symptoms. (13,14) Researchers from McGill University and

the University of Toronto proclaim that "the psychological impacts will be as significant as the physical health impacts from COVID-19, particularly for vulnerable populations." (13) Throughout several self-reported cross-sectional mental health studies, the prevailing consensus is that post-secondary participants' levels of worry, grief, depression, anxiety, and PTSD have increased during COVID-19. (13,14) According to Statistics Canada, younger Canadian participants exhibited more pronounced moderate to severe symptoms of anxiety than older participants throughout the pandemic. (15) Moreover, February 2021 research from Toronto's SickKids Hospital reveals that "greater stress from social isolation, including both the cancellation of important events and the loss of in-person social interactions, was strongly associated with mental health deterioration." (16)

3.5 | Mental Health Prior to Pandemic

Among several studies detailing increased mental health and psychological concerns throughout the pandemic, (17, 18) an exception is a North American longitudinal study with a sample size of 773 post-secondary students – with and without pre-existing mental conditions – examining the differences in mental health responses from May 2019 (pre-pandemic) and May 2020 (pandemic). (13) Although researchers expected participants with pre-existing mental health symptoms to have heightened psychological distress during the pandemic, this hypothesis was disproved. (13) Instead, this group of participants had similar or better mental health during the pandemic. (13) Contrarily, the student participants with no mental health concerns pre-COVID-19 developed significant psychological distress during the pandemic. (13) These results shed light on social isolation's impact on individuals previously presenting with no mental health concerns. However, at this time there is no affirmative explanation for the unexpected improved mental health of pre-pandemic mental health diagnosed participants. (13)

3.6 | Drinking and Substance Use

A cross-sectional anonymous online survey of 1000 youth participants, aged 18-35, studied the correlation of loneliness during COVID-19 with depression/anxiety and alcohol/drug use. (19) Researchers found substantial increases in mental health concerns and substance use due to the pandemic. (19) On top of rising stress and anxiety levels, young adults tend to follow the example set by adults, which is another contributing factor of substance use during COVID-19. (20) As mentioned in a Drug Free Kids Canada article, "It is important for parents to be aware that they may have increased their own substance use to deal with their stress, and as a consequence, their kids may consider that using substances is an appropriate way to cope with their uncomfortable feelings." (20) As reported by a Nanos Research poll summary, a quarter of Canadian participants aged 35-54 increased their drinking patterns during COVID-19 due to stress, boredom, and lack of a regular schedule. (21) As this participant age group includes many post-secondary students' role models, this statistic highlights the mirror effect of substance use as a coping mechanism on youth during troubling times.

3.7 | Screen Time

Excessive screen time is another negative aspect of the pandemic on higher education students' mental health. From keeping up with and communicating through online learning, social media, news/entertainment, and loved ones, young adults have spent much longer staring at devices and sitting in front of screens throughout the lockdown than ever before. (22) According to a current review of screen time and COVID-19, a survey recorded that the pandemic caused a 50-70% increase in internet use, with 50% of that time spent engaging on social media. (23) Research from an online cross-sectional study of 932 students in the United Kingdom shows a correlation between daily screen time and mental health concerns, as measured using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI) tools, reflecting higher cases of anxiety and depression,

respectively. (22) This study accounted for potential confounding factors, and its results are translatable to North American students. (22) Experts suggest 'digital detoxes' and unplugging for hours or days, which typically result in increases in productivity, creativity, connections with loved ones, quality sleep, and decreases in aches/pains. (25) Harvard Pilgrim Health Care claims that "you can feel the physiological effects almost immediately when initiating a digital detox." (25)

3.8 | Sleep Patterns

Given that as screen use, particularly before falling asleep, negatively affects sleep quality, Harvard Health shows that there is also a strong correlation between sleep and mental health concerns. (26) Sleep deprivation is known to impact one's mental health and psychological state. (26) Likewise, individuals with mental health concerns are more at risk for sleep disorders such as insomnia. (26) For instance, studies often compare depression, anxiety, and PTSD with sleep patterns and sleep disorders. (26). Multiple studies conclude that most patients who categorized with one or more mental health concerns also experience sleeping problems or sleeping disorders. (26,27) Generally speaking, sleep problems increase the risk of developing mental health symptoms such as depression. (27) As a McGill University sociology student, Erika MacKenzie, explains in her opinion article speaking on behalf of the student population nationwide, "In conjunction with being drained, the lack of sleep made me more anxious and depressed, further inhibiting my academic performance." (7) Overall, "exposure to stimulating content, mobile phone overuse and phone addiction contribute to hyper arousal in pre-bedtime period and poor sleep quality," which cause excessive daytime sleepiness and contribute to mental health concerns. (27)

3.9 | Self-Harm and Suicide

With severe isolation, loneliness, stress, and negative emotions due to COVID-19, some post-secondary students face alarming consequences, including self-harm and suicide. (4) Throughout the pandemic, youth suicide has become the second leading cause of death in individuals aged 15-24. (4) Research from Providence St. Joseph Health, a non-profit healthcare system in various U.S. states, expresses that citizens are greatly at risk of deaths of despair: deaths from drugs, alcohol, and suicide. (28) As quoted in their 'Projected Deaths of Despair from COVID-19' abstract, "Deaths of despair have been on the rise for the last decade, and in the context of COVID-19, deaths of despair should be seen as the epidemic within the pandemic." (28) Researchers warn of "a grim picture of the struggle with lockdown isolation — a 'mental health pandemic' that should be treated as seriously as containing the coronavirus." (5) Throughout the U.S., schools are announcing severe rises in self-harm and suicides. (4) Notably, "it is worth remembering that more young people will die from suicide and road traffic accidents than COVID-19 this year." (11) In essence, students feel that they have sacrificed more than a year of their youth to protect their elders, and in the process, they have experienced devastating side effects. (11)

3.10 | Available Resources

With the accumulation of complex challenges faced by higher education students, school counsellors should not be the only resource available; instead, post-secondary institutions have an ongoing obligation to monitor their students' mental health, both before and after returning to campus. As the return to on-campus learning becomes a reality for upcoming semesters, post-secondary institutions must take responsibility for their student body and prioritize the mental health of their students. The Mental Health Commission of Canada reports the following:

Three out of every four mental health problems have been first diagnosed between the ages of 16 and 24, when many are in or just out of post-secondary education. In 2020, the COVID-19 pandemic heightened many of the issues students were already facing, making it even more challenging for institutions to support them. (29)

It is imperative for higher education leaders to ac-

knowledge such obligations and to initiate changes on campus, both remotely and in person. Post-secondary students should have multiple methods and resources at their disposal to discuss their well-being, mental health, and other concerns. School counsellors are indispensable; however, "they can't be the only office on campus responsible for students' mental health. Administrators and faculty and staff members all have a role to play in ensuring that students are not only surviving but also thriving." (30) Educational institutions have a duty to perform as it cannot be expected that such a fragile age group can simply return to campus as if COVID-19 never happened. Thus, as the real impact of COVID-19 makes itself apparent, there is an institutional obligation to monitor and provide ongoing outreach and counselling services for as long as the demand warrants.

4 | CONCLUSION

4.1 | Future Research

The COVID-19 pandemic has touched hundreds of millions of people physically and taken the lives of over 5 million individuals, (31) yet the resultant mental and social aspects cannot be ignored. Post-secondary students across North America have experienced incredibly damaging effects to their mental health triggered by social isolation and online learning. This crisis should not be taken lightly as it becomes a growing concern the longer the pandemic continues, and the longer students are kept away from their normal social lives and in-person education. Consequently, long-term mental health concerns arise, including depression, anxiety, PTSD, substance abuse, screen-overuse, and sleep issues. "Education changes the way we perceive the world and behave in relation to others, and this affects our brain directly. The consequences for youth development in the years to come could be vast, with impacts likely on self-control, social competence and logical deduction amongst other cognitive abilities." (11) Higher education institutions are well aware of the mental health damage over the past year. This early research is fuelling their efforts to get students back to in-person learning as quickly as possible without circumventing safety. Nonetheless, there is an urgent need for further research on COVID-19's long-term impact on the mental health of post-secondary students. Then, armed with facts, prevention and intervention by schools, communities, and government must be prioritized to preserve the well-being of our youth.

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NARRATIVE REVIEW
McGill Journal of Medicine

Prevention of Hamstring Injuries in Male Soccer Athletes

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ABSTRACT

Background: One of the most frequently injured muscle groups in soccer is the hamstring group. Soccer players have high rates of hamstring injury (HSI) due to frequent sprinting, changes in direction and similar high-risk activities. Such movements put immense stress on the hamstrings which can lead to injury. Over the last decade, at least four different HSI prevention programs and techniques have been explored in research. The purpose of this review is to assess the effectiveness of these methods.

Methods: Studies in this review were collected using multiple database searches of PubMed. A total of six studies were selected, all either randomized controlled trials (RCTs) or cluster-RCTs. The selected trials were from various soccer leagues in Denmark, Japan, the Netherlands, and the United States.

Results: The most prevalently studied method is the Nordic hamstring exercise (NHE). Studies that utilized the NHE, either as a standalone or within a program, reduced the risk of HSI by 15-71%. In addition, effective programs were characterized by progressively increasing the difficulty of exercises and high compliance rates.

Conclusion: Studies that utilized the NHE showed effectiveness in the prevention of hamstring injuries in male soccer athletes. Based on the limited research available, it is unclear whether adding other exercises to prevention programs further reduces injury risk. More research is needed to explore new and existing prevention methods in a variety of populations and regions.

KEYWORDS
Hamstring injury, Prevention, Exercise, Soccer

1 | INTRODUCTION

Soccer, also known as football, is regarded as one of the most popular sports in the world. Different soc-

cer competitions, premier leagues, and cups are held every year. Unfortunately, a soccer player sustains an average of two injuries per season. (1) Common soccer movements such as prolonged running, changes in acceleration, sprinting and kicking can all lead to injury. (2) Hamstring injuries are the most prevalent types of injury among all players ranging from youth to professional players. (3) It accounts for around 15-20% of all soccer injuries. (1, 4)

The hamstrings include the biceps femoris, semimembranosus and semitendinosus muscles, (5) which allow for knee flexion and hip extension. The most common type of hamstring injury is a muscle strain. (6) This occurs when one or more of the muscles tears, either partially or completely. Studies have shown that injury often occurs during the terminal swing phase. (7) Additionally, there are many factors that increase the risk of hamstring injuries., the most common of which are older age, fatigue, lack of flexibility, previous HSI, and muscle imbalance. (8,9)

Different hamstring injury prevention programs have been studied, tested, and implemented in various soccer leagues across the world. One major exercise used for building hamstring strength is the Nordic hamstring exercise (NHE, Fig. 2). (10) The NHE is part of both the 11 and 11+ FIFA prevention programs. It is a partnered exercise where the athlete kneels with their torso maintained upward, whilst the partner immobilizes the athlete's ankles and legs through pressure. The athlete tries to stay upright for as long as possible, maximizing the eccentric load on the hamstrings. The upper extremities are used to maintain balance. (10) Other exercises used to strengthen the hamstrings include bounding, lunges, and squats. (10, 11) These exercises are also seen in some HSI prevention programs.

Injuries have significant consequences on team performance. One study found injury rates to be associated with league ranking, performance in cups, and points per match. (12) A definitive method for preventing hamstring injury in soccer is necessary, as hamstring injuries have increased 4% annually from 2001 to 2016. (13) Some studies have had success with prevention programs, but evidence for a definitive method is limited. (10, 14, 15) The aim of this review is to compare existing prevention programs to determine what factors make up effective interventions in the prevention of hamstring injuries.

2 | METHODS

The study examination process consisted of a general database search and review of the available studies. A primary search was conducted on PubMed. General searches were conducted with the key words 'hamstring injury', 'soccer injury', 'hamstring injury prevention' and 'soccer injury prevention'. Multiple searches were conducted over several months as part of the review process. Articles were included in the review if they were published between June 2011 and June 2021, reported data on hamstring injury incidence, and were randomized controlled trials (RCTs) or cluster-RCTs.

The characteristics examined in each selected study included age, location, compliance rate (%), study duration, intervention method and frequency of intervention. Any other factors that were not present across all selected studies or lacked clarity were excluded from the review and are briefly addressed in the discussion. The specific characteristics of individual prevention programs reviewed for this article include joint movements, types of movements, exercises, emphasized skills and whether a program increased in difficulty over the course of the study.

The study's effectiveness in preventing hamstring injury was quantified by the incidence rate ratio (IRR). The risk ratio was calculated by dividing the injury incidence in the intervention group (IG) by the injury incidence in the control group (CG). Injury incidence was calculated by the number of hamstring injuries per 1000 hours of soccer played. Some trials provided data for injury incidence and/or risk ratio. An IRR of less than 1 suggests a reduced risk of hamstring injury. An IRR close to or greater than 1 suggests minimal difference in risk of hamstring injury. A statistically significant risk reduction was determined by the provided confidence intervals and/or p-values ($p<.05$).

3 | RESULTS

All studies implemented HSI prevention programs. One study implemented the FIFA 11+ Program, which is also designed for the prevention of other lower body injuries. (14) Only data concerning the hamstrings were included in the review. A total of 56 studies were identified, and six studies were selected for the review. All six studies were RCTs, meaning that participants were randomly assigned to either the control or intervention group. Three were clustered RCTs. (10, 16, 17)

3.1 | Study Characteristics

The characteristics of selected studies are listed in Table 1. The selected studies reflected various regions, age groups, and competition levels. Three studies were conducted in the Netherlands, one in the United States, one in Denmark, and one in Japan. (10, 14-18). Ages were as young as 15 years old in Hasebe et al., which conducted its trial at the high school club level. (18) Another young age group was seen in Silvers-Granelli et al., at the collegiate level. (14) The remaining four studies consisted of adult amateur soccer players. (10, 15, 16, 17) Compliance was above average for most of the studies, with three reporting over 88%. (10, 15, 18) The trial period for all studies was one soccer season. The frequency of intervention was used was similar across studies with minor variations based on the time of season (1-3 times/week). Only van Beijsterveldt et al. did not specify the frequency of the intervention.(16)

3.2 | Prevention Programs

The review examined the Bounding Exercise Program, FIFA11+ Program, The11 Program, and the Nordic hamstring exercise. The joint movements, exercises, emphasized skills, and exercise progression were considered when comparing programs. Different exercises and joint movements will target different muscle groups and have varying effects, which can be compared for effectiveness. The emphasized skills can provide insight on what the main goal of the program was. The data for these features is listed in Table 2 All six programs consisted of some eccentric exercises. The bounding exercise program (BEP) included walking, lunges, and drop lunges (weeks 1-6), all which incorporate concentric and eccentric movements. (17) It then continued with bounding exercises for the remainder of the study. (17) The 11 and FIFA11+ programs consisted of many of the same exercises. (14, 16) They included the sideways bench, NHE, single-leg stance, jumping and bounding. The FIFA11+ also had three levels of squat exercises and running exercises. The running exercises were conducted before and after the main strength exercises. (14, 16) van der Horst et al. and Petersen et al. both used the Nordic hamstring exercise as the main intervention. (10, 15)

The programs all made participants perform similar joint movements, despite the differences in exercises. Knee flexion was included in all six programs, as it is the main motion utilized in NHE, lunges, and other exercises. Other motions included hip flexion and extension, hip rotation, and knee extension. These movements were seen in exercises such as lunges, single-leg stance, and bounding. (10, 14-18) Petersen et al. only used the Nordic hamstring exercise, so knee flexion was the main joint movement of that intervention. (10)

There was great variation in the skills emphasized by each intervention program. There were two programs that mainly focused on the NHE emphasized technique, increasing hamstring resistance, and maintaining maximum eccentric load. (10, 15) The programs established by FIFA (The11, 11+) both emphasized a similar skillset, but the level of detail and difficulty was increased in the 11+ program. (14, 16) 11+ also included a focus on hamstring resistance, neuromuscular control, plyometrics, and agility. (14) The BEP mainly focused on increasing bounding distance and repetitions. (17)

All but one program (The11) had some level of progression in difficult throughout the study period (16). Progression consisted of increasing the number of session (per week), number of sets per session, the number of repetitions per set and/or the difficulty of the exercises. (10, 14-18) For instance, one of the exercises in the FIFA 11+ program is the bench, which is a static exercise where the player holds a plank position. However,

Study	Sample Size	Age	Location	Compliance	Study Duration	Frequency	Intervention	Player Level
Silvers-Granelli et al. (13), 2015	1525	18-23	United States	Moderate	1 season	3 times per week	FIFA 11+ Program	Collegiate
Petersen et al. (14), 2011	942	23.5 (avg)	Denmark	91%	1 season	1-3 times per week	Eccentric Training	Adult Amateur & Professional
van der Horst et al. (16), 2015	579	20-29	Netherlands	91%	1 season	1-2 times per week	NHE* only	Adult Amateur
van Beijsterveldt et al. (18), 2012	456	20-29	Netherlands	73%	1 season	Not listed	The11 Program	Adult Amateur
van de Hoef et al. (19), 2019	400	17-31	Netherlands	71%	1 season	2-3 times per week	BEP*	Adult Amateur
Hasebe et al. (20), 2020	259	15-18	Japan	88%	1 season	1-2 times per week	NHE* only	High School

*NHE: Nordic Hamstring Exercise, BEP: Bounding Exercise Program

TABLE 1 Study Characteristics

this exercise changes to a dynamic exercise (alternate legs) and then a modified version (one leg lift and hold) as the study progresses. (14)

3.3 | Study Effectiveness

Injury incidence and injury risk ratio (IRR) data are listed in Table 3. Van Beijsterveldt et al. found that its intervention increased hamstring injury risk (RR, 1.36). (16) The injury incidence (IR) was higher in the intervention group than the control group. This study also conducted trials for other lower extremity injuries. Data for only the hamstring group was calculated by multiplying the total injury incidence rate by the injury location.

Two studies had a minimal decrease in hamstring injury risk. Van de Hoef et al. had a 19% decrease in injury risk (RR, 0.81 [95% CI, 0.46-1.75]). (17) Hasebe et al. had a 15% decrease in injury risk (RR, 0.85, [95% CI, 0.26-4.97]). (18) In both studies, the IR values were similar, so there was a similar rate of injury in the two study groups. In Hasebe et al., the incidence rate for both the control and intervention groups were the lowest values of any study (CG, 0.104; IG, 0.088). (18)

Three had a significant decrease in hamstring injury risk. Silvers-Granelli et al. had a 63% decrease in injury risk (RR, 0.37 [95% CI, 0.21-0.63]; P<.0001). (14) Van der Horst et al. had a 69% decrease in injury risk (RR, 0.31 [95% CI, 0.11-0.72]; P=.005). (15) This study had the second-lowest incidence rate in its intervention group of any study (IR, 0.250). (15) Petersen et al. had a 71% decrease in injury risk (RR, 0.29 [95% CI, 0.15-0.57], P<.001). (10) It reported only 0.380 hamstring injuries per 1000 hours of soccer. (10)

Study	Joint Movements	Types of Exercises	Exercises	Emphasized Skills	Increased Difficulty
Silvers-Granelli et al. (13), 2015	Hip rotation, Knee flexion, Hip flexion, Trunk bending	Running, Strength, Eccentric, Plyometric, Balance	Running, The bench, Nordic hamstrings, Single-leg stance, Squats, Jumping, Bounding	Hip stability, Eccentric exercises, Hamstring resistance	Yes
Petersen et al. (14), 2011	Knee flexion	Eccentric	Nordic hamstrings	Hamstring resistance, Maximum Eccentric Load	Yes
van der Horst et al. (16), 2015	Knee flexion	Eccentric	Nordic hamstrings	Maximum eccentric load, Minimal concentric load	Yes
van Beijsterveldt et al. (18), 2012	Hip flexion, Hip extension, Knee flexion, Knee extension	Ecccentric, Core stability, Plyometric	The bench, Nordic hamstrings, Single-leg stance, Jumping, Bounding	Hip stability, Eccentric exercises, Hamstring technique	No
van de Hoef et al. (19), 2019	Hip flexion Hip extension Knee flexion Knee extension	Concentric, Eccentric, Plyometric	Walking lunges, Triplings, Drop lunges, Bounding	Increase bounding distance, Repetitions	Yes
Hasebe et al. (20), 2020	Knee flexion, Knee Extension	Eccentric	Nordic hamstrings	Isometric knee extension, Flexion strength, Flexibility	Yes

TABLE 2 Prevention Programs

4 | DISCUSSION

4.1 | General Findings

Each study examined several factors that could influence the risk of hamstring injury. Surprisingly, many of the factors did not have a significant impact. The age range was similar for most of the studies, around 20-31 years old. (10, 14-18) In Hasebe et al., the sample consisted high school players. (18) As a result, the age range was lower than in other studies. On the other hand, the other studies were conducted in adults at an amateur or professional level. Hasebe et al. may have had injury incidence rates that were significantly lower than in the other studies due to the younger age of the subjects they studied. The control IR was 0.104, which is much lower than the second-lowest, 0.800. (15, 18) It had a 15% reduction (RR, 0.85 [95% CI, 0.26-4.97]), but the reported confidence interval suggests this was insignificant. (18)

Similarly, van de Hoef et al. had a 19% reduction in risk (RR, 0.81 [95% CI, 0.46-1.75]). (17) The subjects were adult amateur level players. The injury incidence for their control data was similar to other studies of the same age group. The reported confidence interval for van de Hoef et al. included 1, therefore the reduction was statistically insignificant.

Lack of compliance influencing a study's results was unlikely, as five out of six studies had a compliance rate of over 70%. (10, 15-18) The duration for all the re-

Study	Sample size (total players)	Injury Incidence*		IRR [95% CI]	p-value	Reduction
		Control	Intervention			
Silvers-Granelli et al. (13), 2015	1525	1.244	0.454	0.37 (0.21-0.63)	<.0001	63%
Petersen et al. (14), 2011	942	1.310	0.380	0.29 (0.15-0.57)	<.001	71%
van der Horst et al. (16), 2015	579	0.800	0.250	0.31 (0.11-0.72)	.005	69%
van Beijsterveldt et al. (18), 2012	456	1.300	1.766	1.36 (N/A**)	N/A**	N/A
van de Hoef et al. (19), 2019	400	1.390	1.120	0.81 (0.46-1.75)	N/A**	19%
Hasebe et al. (20), 2020	259	0.104	0.088	0.85 (0.26-4.97)	.83	15%

*Measured in hamstring injuries per 1000 hours of soccer.

**Data not provided

TABLE 3 Program Effectiveness

viewed studies was one soccer season, likely because they were RCTs. (10, 14-18) Cohort studies often last longer, as they track the progress of subjects over several years. Studies with significant reduction in risk increased the frequency of the intervention as time progressed.

4.2 | Successful Studies

Petersen et al., van der Horst et al., and Silvers-Granelli et al. were three studies with adult amateur level players. (10, 14, 15) They showed risk reduction over 62%. The reported p-values were below .05 for all three studies. (10, 14, 15) Based on the p-values, these three programs were effective in the prevention of HSI.

The design and implementation of a prevention program provides insight into what makes an effective intervention. Several trends were seen in the three effective programs, which reduced injury risk by as much as 71%. (10, 14, 15) Notably, all three programs utilized the Nordic hamstring exercise. Silvers-Granelli et al. included other exercises, such as flexibility exercises and other lower-leg movements as part of FIFA11+. (14) However, the intervention program used in Petersen et al., Hasebe et al., and van der Horst et al. only used the NHE. (10, 15, 18) A recent systematic review that explored NHE effectiveness found the intervention to significantly reduce injury risk. (19) It focused on examining the characteristics of studies and the details of NHE training protocols. However, the review focused exclusively on NHE-based interventions.

Successful programs also incorporated increased difficulty in the exercises. For example, the program used by Silvers-Granelli et al. included three variations for each exercise. (14) The exercises included several different joint movements, including hip rotation, knee flexion, hip flexion, and trunk bending. In van der Horst et al., the first five weeks were a build-up phase. During this phase, the number of sets and repetitions gradually increased every week. In contrast, the program utilized by van Beijsterveldt et al. The 11 did not increase difficulty throughout the trial. (16) As a result, this study did not have a build-up phase to the intervention. It reported the intervention to be ineffective in preventing HSI. (16)

4.3 | Limitations

The most significant limitation of the review was the limited research available. Many of the recent studies that investigate hamstring injuries assess strength characteristics rather than injury incidence rates. Consequently,

these studies could not be used in the review. This limits the ability to generalize the findings.

5 | CONCLUSION

The studies investigated in the review incorporated different programs, features, and exercises with the goal of preventing and reducing HSI. They all had different rates of success which were dependent upon several characteristics, most notably the intervention method. The studies that implemented the NHE intervention reduced injury risk by as much as 71%. Injury risk also decreased in studies that included progressively difficult exercises and high compliance. (10, 14-18)

More research is needed to better understand effective methods for HSI prevention. Specifically, more randomized controlled trials in a variety of soccer leagues across different divisions. It is important that hamstring injury be studied to reduce hamstring injury risk in soccer players.

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NARRATIVE REVIEW
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An Avant-garde Approach to Life: Reviewing the Current Applications of 3D Bioprinting

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ABSTRACT

Introduction: The promise of bioprinting tissue constructs that could potentially serve the same function in the human body as native tissues has taken the world of regenerative medicine by storm. The current review describes system-wide clinical applications of three-dimensional (3D) bioprinting and aims to address ethical and social considerations, while also discussing the scope of this technology in the near future.

Discussion: 3D bioprinting is believed to present new approaches to conventional treatment; offering the advantage of customization and on-time availability. It facilitates simultaneous deposition of appropriate bioinks and biomaterials onto scaffolds which can then be employed to develop tissue fabricates that can potentially mimic native tissues in both structure and functionality. It has been extensively employed to regenerate viable tissue constructs of skin, bone, cartilage, vasculature, myocardial tissue and heart valves, nervous tissue, lung and tracheal tissue, liver, pancreatic, and corneal tissue.

Conclusion: To obviate the current restrictions associated with this technology, it is imperative to understand where we currently stand in terms of current clinical applications of 3D bioprinting. This technology is anticipated to contribute significantly to the fields of tissue engineering and regenerative medicine (TERM), where it can be employed to fabricate functional tissues that can simulate their counterparts in the human body.

Relevance: The increasing disparity between organ demand and supply as well as the shortcomings associated with antiquated approaches to treatment call for utilizing 3D bioprinting to develop viable tissue constructs.

KEYWORDS

Bioprinting, Tissue Scaffolds, Biomaterials

1 | INTRODUCTION

Organ transplantation is the ultimate approach for the treatment of end-stage diseases. A precarious imbalance between organ demand and organ supply accentuates the need for bioprinting viable tissue fabricates that can simulate the physiological and anatomical features of target tissues and can serve the same function *in vivo* as their counterparts in the human body. 3D bioprinting is defined as the process of depositing biocompatible materials in a layer-by-layer manner to develop tissues that can mimic the properties of living cells (1). The creation of tissue constructs is performed by combining computer assisted design (CAD) with computer assisted manufacturing (2) to meticulously fashion appropriate biomaterials and bioinks into tissue substitutes; and provides considerable control over their structure, reproducibility, and functional accuracy (3). This technology offers concurrent printing of various types of cells in defined spatial locations, making its use in regenerative medicine of paramount importance (4). This review aims to highlight current applications of 3D bioprinting in clinical settings as well as pharmaceutical and cancer research; and, moreover, will recount socio-ethical concerns, future perspectives and possibilities.

2 | APPROACHES TO 3D BIOPRINTING

Techniques used to bioprint tissue constructs are grouped into various categories based on their printing principles. These categories include inkjet-based, pressure-assisted, laser-assisted bioprinting techniques, stereolithography, and extrusion based bioprinting (5); and each technique finds its application in printing specific tissues, having particular advantages and shortcomings (6). Salient features of commonly employed approaches to bioprinting have been summarized in Table 1. Bioinks, which are a crucial component, refer to cellular aggregates deposited on or within scaffolds or a construction of cells that may consist of bioactive components and biomaterials (7). Clinical applications of 3D bioprinting have largely been restricted by the lack of adequate bioinks available for printing viable target tissues (8) and limitations associated with bioprinting techniques, including poor resolution and deformation of cells due to shear stress (9).

3 | CURRENT APPLICATIONS

3D Bioprinting has surfaced as a major scientific breakthrough in the rapidly advancing fields of regenerative medicine and medical research (10). Over the last two decades, it has challenged the obsolescence of conventional treatment, offering an effective solution to problems such as insufficient matching organ donors, post-transplant immune rejection, and infection. Current major applications of 3D bioprinting have been summarized in Figure 1.

4 | IN TISSUE ENGINEERING AND REGENERATIVE MEDICINE

4.1 | Skin

Skin, being the outermost layer, is extremely susceptible to damage resulting from disease, trauma, burns, or surgery, making skin restoration imperative post-trauma or injury. The bioink employed in skin engineering is an optimal combination of cells, typically keratinocytes and fibroblasts collected from the patient, and collagen, which is used as hydrogel to imitate the extracellular matrix (ECM) (11). This combination is then printed using the appropriate bioprinting technique following digital photographs or thermal images (11). Skin bioprinting becomes particularly important in the treatment of full-thickness burns where, in the place of severe burn dressings, multilayered skin substitutes are being developed using cells and ECM combined as bioinks to counter the expense of treatment and scarcity of donors (12). Although skin bioengineering offers a promising solution to the shortcomings of autotransplantation, allotransplantation, and xenotransplantation, which include transplant rejection, risk of infection, and limitation to

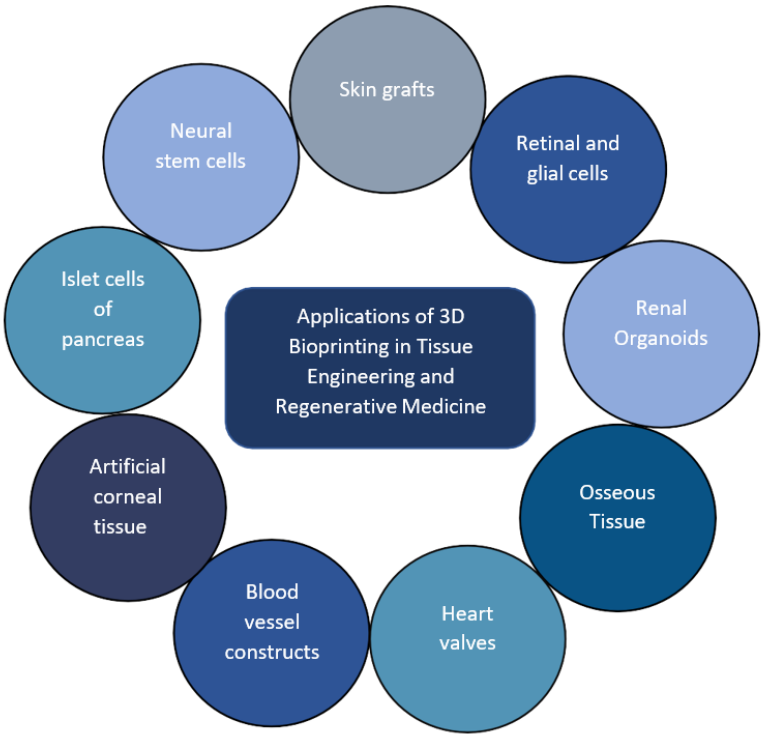

FIGURE 1 A summary of major applications of 3D bioprinting in Tissue Engineering and Regenerative Medicine

minor injuries (13), the clinical application of skin constructs is largely limited by the challenge of how to vascularize and innervate said constructs (14).

4.2 | Bone

Although known to have highly regenerative and reparative properties, osseous tissue often fails to heal large-scale bone trauma completely by itself (15), whereby clinical intervention becomes necessary to ensure normal bone function; and 3D bioprinting of bone tissue offers numerous advantages pertaining to control over porosity, biocompatibility, mechanical strength, and degradability (15). Bone tissue is comprised of osteoblasts and inorganic ECM, where inorganic ECM is composed primarily of hydroxyapatite (HA) (16). HA and tricalcium phosphate ceramics are commonly employed as bone scaffolds, offering a favorable environment for cells like osteoblasts and mesenchymal stem cells (MSCs) to grow (17). Importantly, constructs synthesized using scaffolds of HA and polycaprolactone (PCL) that are implanted into skull defects exhibit vascularization, integration with surrounding tissue, and provide support for new bone formation (18). Currently, such bone graft substitutes are predominately cell-free and rely on host progenitor cells to initiate the process of bone recuperation (18). Constant enhancements to bone constructs are being made by the addition of effective growth factors, investigation of better biomaterials, and improvement of bioprinters to ensure not only implantation of these constructs but also their sustainability over time. Of great importance when considering enhancements to bone constructs is successful vascularization, which is crucial for the supply of nutrients and has been achieved via *in vivo* strategies that utilize smart scaffolds and pre-vascularized grafts (19).

4.3 | Cartilage

Commonly occurring degenerative cartilage diseases, such as osteoarthritis, along with the limited regenerative potential of articular cartilage call for cartilage bioprinting to combat the restrictions associated with current treatment options. Because cartilage is an avascular tissue, this makes it one of the simplest structures to be successfully bioprinted. Similar to the anatomical and physiological properties of chondral tissue, 3D bioprinting is able to deposit chondroprogenitor cells or differentiated chondrocytes along with suitable growth factors in biocompatible scaffolds to attain the functionality of native tissues (20). Although chondrocytes are predominantly used for cartilage bioprinting (21), the use of stem cells instead offer a better opportunity to improve cartilage regeneration due to their immune privileged status and paracrine activity (22). For the bioprinting of cartilage, bioinks utilized for the synthesis of hyaline cartilage are most commonly alginate and agarose hydrogels seeded with MSCs, and GelMA (gelatin methacrylate) for the synthesis of fibrocartilage (23).

4.4 | Cardiac Tissue

Significant research efforts in 3D bioprinting have focused on ways to bioprint cardiac tissue in hopes of better treating cardiovascular disease, which is the primary cause of death worldwide (24). As far as bioprinting of cardiac tissue is concerned, conservation of mechanical and electrical properties of cardiomyocytes remains a key requirement (25). Tissue spheroids have been constructed by co-printing human vascular endothelial cells (HUVECS) and cardiac cells which, when fused together, establish a cardiac patch after approximately three days that is able to beat in sinus rhythm (20). Importantly, contractility and conductivity of cardiac constructs are reported to be improved by applying electrical stimulation during the culture of these constructs (26). Despite prosthetic valves previously used in treating valvular heart disease being successfully substituted by 3D printed heart valve conduits (synthesized using methacrylated and methacrylated gelatin) (27), bioprinted cardiac tissue, as of now, is far from implantation-ready at present stage. (20)

4.5 | Nervous Tissue

The central nervous system represents considerable intricacy of structure, immense complexity of function as well as a weak capacity for regeneration and, therefore, poses a major challenge for the synthesis of viable neural tissue constructs. Impressively, human cortical spheroids (hCSs) containing neurons from deep and superficial cortical layers have been developed from pluripotent stem cells, and, moreover, are able to exhibit spontaneous activity, form synapses, and recruit networks of astrocytes (28). Alternatively, a polysaccharide-based bioink comprising of alginate, carboxymethyl-chitosan and agarose used in conjunction with direct-write printing of human neural stem cells (NSCs) facilitates *in situ* differentiation into functional neurons and supporting neuroglia (29). More recently, a poly(3,4ethylenedioxythiophene)/chitosan/gelatin (PEDOT/Cs/Gel) scaffold used for 3D culture of NSCs has been reported to not only promote the adhesion and proliferation of NSCs but also facilitates their differentiation into neurons and astrocytes (30). Since only a few studies have been reported in the context of bioprinting nervous tissue, rigorous efforts are needed to further establish stable and functional nervous tissue constructs. Neural bioprinting, if and when applied clinically, may potentially solve the colossal challenge of innervation of bioprinted tissues.

4.6 | Lung and Tracheal Tissue

3D bioprinting offers an advanced platform for concurrent deposition of multiple cell types in an accurate morphology so that the prerequisites for constructing lung-like tissues can be realized and appropriate scaffolds can be designed. Greater progress has been made in bioprinting tracheal tissue, however, epithelialization and vascularization of grafts remain as primary concerns (31). Even greater obstacles remain with regards to 3D printed lung tissue, as scaffolds should allow for proper

gas exchange and account for other mechanical properties such as lung compliance, elasticity and recoil. To tackle these challenges, bioprinting is being utilized to develop a human air-blood tissue barrier analogue composed of alveolar epithelial type II cells, endothelial cells, and BM Matrigel^{TM} via a valve-based bioprinting approach (32). Making this endeavour feasible is acellular collagen, Matrigel^{TM} and alginate, which are commonly utilized as bioinks for the 3D printing of lung tissue due to their favorable elastic moduli (33).

4.7 | Blood Vessels and Cellular Components of Blood

Printing biomimetic blood vessels remains a formidable challenge as a high resolution is required to print these extremely fine structures that must endure high stress and pressure without damage to the integrity and stability of the printed cells. Bioprinting blood vessels can be achieved by (a) the development of bulk matrices with integrated channels as perfusable matrices, (b) cell patterning into line structures for self-assembly of an interconnected vessel system, or (c) generation of free-standing tubular structures serving as artificial vessels (34). The addition of magnetically controlled nanoparticles (NPs) to bioink has been reported to keep the diameter of the blood vessel reduced to that of a capillary, yet, the use of magnetic NPs and magnetic fields in the positioning of vessel constructs within tissue is still in its infancy and requires greater investigation (35). Because a limited number of techniques are available to vascularize bioprinted tissue constructs, this hinders their implantation *in vivo* as adequate blood supply is needed for proper supply of nutrients and waste removal. So far, spheroid bioprinting upon appropriate biomaterial beds or direct deposition of cells on hydrogel scaffolds are two approaches employed to construct vascular structures. The former technique, however, results in constructs with low mechanical strength and stability (36) and, more generally, considerably more research is needed to generate functional and viable blood vessel constructs that can stand on their own. As far as cellular components of blood are concerned, a novel soluble nanobiotechnological complex formed by crosslinking hemoglobin, superoxide dismutase, catalase and carbonic anhydrase can serve all three functions of red blood cells. These include oxygen-carrying and carbon dioxide-carrying properties along with the ability to remove oxygen radicals, thus enabling successful preparation of artificial red blood cells (37).

4.8 | Renal Tissue

Kidney damage primarily due to renal disease or secondary to Diabetes Mellitus, hypertension, or obesity that results in impaired kidney function is a grave health concern worldwide. Due to its intricate and complex structural morphology, only specific portions of the nephron have been synthesized, which are indeed similar in anatomy and physiology to native renal tissue. These constructs are derived from epithelial cells of the proximal convoluted tubule, supported by a collagen type IV interface of renal fibroblasts and endothelium (38). By leveraging human pluripotent stem cells (hPSCs) and human induced pluripotent stem cells (hiPSCs) (39), dissociated and re-aggregated embryonic kidneys can be used to develop compact renal organoids that not only contain functional nephrons but follow the course of development of a normal kidney. Despite this, the collecting ducts in these organoids are still absent of a drainage system. Although currently employed to study the effects of drug toxicity, risk assessment, and the development of new drugs (40), the production of renal tissue bioprints demands approaches that cater to both the filtration and homeostatic function of kidneys.

4.9 | Liver

Despite the inherent and remarkable capability of the liver to regenerate and restore its normal function post hepatic injury, the recuperative process can, on occasion, fail to initiate or becomes dysfunctional, leading to pathogenesis and ultimately hepatic failure (41). Impairment of liver function due to chronic liver disease, alcohol abuse, cancer, and other liver insults stipulates the need for developing liver tissue fabricates that ful-

fil the physiological and structural demands of the original tissue. Limited progress in bioprinting viable liver tissue has prompted the development of 'liver-on-a-chip' and microplatform bioreactors, which offer a favorable microenvironment that simulates *in vivo* conditions and make microtechnology a promising tool to bioprint tissue substitutes that can mimic the complex functions and architecture of hepatic tissues (42). For example, Organovo has utilized an extrusion-based bioprinting technique to develop a 3D printed hepatic tissue construct that sustained functionality for up to 4 weeks (43). Additionally, endothelial cells have been combined with primary hepatocytes to achieve vascularization (36). Although the printed models did not exhibit accurate structural morphology, the successful use of endothelial cells has given way to the possibility of developing a fully vascularized and functional hepatic model of the liver that can potentially be implanted (36).

4.10 | Pancreas

The World Health Organization declares that approximately 1.6 million deaths result from diabetes mellitus each year (44). Raised blood glucose levels, which are typically regulated by the pancreas, can cause vascular damage and often result in nephropathy, retinopathy, hypertension, stroke, and neuropathy (45). 3D bioprinting focuses on synthesizing a construct to implant allogeneic islet cells that may better regulate pancreatic function and counteract the debilitating effects caused by diabetes (46). One technique, named extrusion bioprinting, is able to utilize alginate and methylcellulose (Alg/MC) as a bioink to fabricate tissue constructs with accurate morphology, insulin-secreting properties and the ability for insulin to diffuse through the scaffold, however, it also results in decreased viability and fragmentation of the printed islets which eventually undergo apoptosis (47). To address this, co-axial bioprinting technology allows islet cells to be co-printed with endothelial progenitor cells and T cells in order to improve vascularization and viability (46). The bioprinting of a fully functional pancreas is still under investigation and much more research is needed to develop appropriate biomaterials that support and facilitate insulin production. If its potential is realized, 3D printing of viable pancreatic tissue may change the course of treatment for type 1 diabetes mellitus.

4.11 | Cornea

Because the cornea is an avascular structure, bioprinting techniques are deemed a promising alternative to the complications associated with corneal transplantation. Restoration of vision in cases of corneal blindness is predominantly performed via corneal transplants, yet the ratio of corneal donation to patients in need for such transplants is immensely low (less than 1:70 of cases) (48) and calls for investigating novel treatments to cover the shortage of donors (48). Laser assisted bioprinting to fabricate corneal constructs has been carried out by depositing limbal epithelial stem cells (LESCs) and human adipose tissue-derived stem cells (hASCs) using collagen 1 and recombinant human laminin as a basis for these bioinks. Along with corneal constructs, biofabrication of retinal ganglion cells, glia as well as of retinal pigment epithelium has been described (49). Moreover, 3D bioprinting provides the advantage of customizing corneal implants as well as precise control over structure and refractive ability, which makes the use of such implants in treating corneal blindness of immense importance.

5 | IN CLINICAL AND CANCER RESEARCH

Tissue bioprints have been used extensively to study the effects of drug toxicity and the pathophysiology of different diseases. There is a pressing demand for establishing human tissue models that can accurately recapitulate the cellular and physiological complexities of *in vivo* tissues so that the pathogenesis of different disease states can be studied more efficiently; and for drug response and toxicity to be investigated more effectively (50). Restrictions associated with cancer research carried out on 2D cultures and murine mod-

els, which include failing to develop tumor microenvironments (TME) and failing to recapitulate human tissue morphology, have been addressed by 3D bioprinted models (51) with the added advantage of permitting the study of personalized cancer treatment (52). Engineered hydrogel tumor models present an opportunity to recapitulate the *in vivo* environment providing deeper insight into cancer cell behaviour (53), for example, the recently described hyaluronan (HA)-oxime breast cancer model that effectively represents the *in vivo* phenotype (54).

Bioprinting may also be employed to prepare drugs and drug delivery systems (55). Predicting the efficacy and toxicity of new drugs will hasten the process of introducing new and improved drugs into the market, as biofabricated tissue constructs will not only allow for testing of these drugs on native-like tissues but will also provide an opportunity to study physiological responses to their effects (40). Moreover, patient-specific models are also being utilized to study surgical planning, to rehearse surgical procedures, and for medical and patient education (56).

6 | IN SITU BIOPRINTING

The objective of 3D bioprinting is to synthesize viable tissue constructs outside of any living organism that can be successfully implanted within the body (57). *in situ* bioprinting, also called *in vivo* bioprinting, allows the printing to take place directly at the site of defect or injury (58) and has been practiced in the context of skin, where inkjet bioprinting technology (59) has been used to bioprint *in situ* over skin using an inkjet-based bioprinter (60). Although these investigations suggest immense potential for bioprinting tissues on site, further investigation is needed to make it practical for application.

7 | FUTURE PLANS AND POSSIBILITIES

3D bioprinting is anticipated to contribute significantly to the development of personalized drugs, which will be particularly effective in overcoming the issue of pharmacogenetic polymorphisms (61). Ex vivo 3D Bioprinting also provides the opportunity to customize prostheses and dental implants in accordance with the needs of the patient (62). The most anticipated advancement of 3D bioprinting is predicted to be made in the field of tissue engineering and regenerative medicine (TERM), where these printing technologies can be employed to construct viable and functional tissues. However, current research limits the clinical application of synthesized tissue constructs as the significant challenges of vascularization, innervation, *in vivo* survival, and functional sustainability remain. If biofabrication of complex tissues is to become successful in the future, this would bridge the gap between organ demand and organ donation (63); and better test the efficacy of drugs directly on a patient's printed tissue strip (62). Although there are many questions that remain unanswered about the clinical application of this technology, one cannot deny the immense potential it holds if a transdisciplinary effort is carried out to circumvent the aforementioned challenges.

8 | LIMITATIONS

Major limitations associated with 3D bioprinting of tissues and organs are vascularization and maintenance of post-print sustainability. Bioprinting thick tissues that are viable and functional also remains a colossal challenge (64). Although 3D bioprinting offers a novel approach to conventional treatment, and the media heavily promotes the timely emergence of organ bioprinting, immense work needs to be done for it to become applicable in clinical settings (65). Besides biological concerns, monitored use of these printers and patent concerns also need to be addressed (66). An important question, in this case, is whether bioprinters will be a patentable or a non-patentable technique? The answer to this question remains, along with other legal concerns regarding the printers and the technique itself (67).

9 | SOCIO-ETHICAL VIEW

As the innovations of 3D bioprinting gain traction, it becomes crucial to highlight ethical and social concerns, and to devise policies regarding the application and distribution of this technology (68). Firstly, the research community is still unable to determine as to if or when organ biofabrication, in its entirety, will be possible. *in vivo* testing of bioprinted tissues and organs in humans is another area of major concern: there is the question of who will be responsible if printed tissue undergoes necrosis or fails to conform to its bodily environment, ultimately leading to infection at the site of implantation? Would there be a certain limitation as to what should and should not be bioprinted? In the context of complications, who will be held accountable for the treatment opportunity that was lost in favour of implanting biofabricated tissue (69)? Currently, there is an absence of international directives and a regulatory outline related to experimental testing of bioprinted tissue in humans. Concerns over ownership and value of these biofabricated constructs by different parties involved in their development also needs to be addressed (70), as does the financial cost for those who opt for biofabricated and personalized tissues and implants as treatment (71). Taking into account all these concerns, a collective effort of researchers, lawyers and policymakers is needed to avoid exploitation of this potentially revolutionary technology (72).

10 | CONCLUSION

3D bioprinting opens new doors in the field of regenerative medicine and research in general by providing an opportunity to print viable tissue constructs. Although this technology can imitate the function and architecture of their counterparts in the human body, much work needs to be done to make it clinically applicable and to sustain post-print viability of these tissues, so that they retain functionality and maintain reproducibility. Ethical concerns and patent issues need to be resolved before it can be made available as a treatment plan; and a colossal interdisciplinary collaboration is needed to bring this technique from bench to bedside.

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TABLE 1 A summary of salient features of major bioprinting techniques along with their clinical applications

3D Bioprinting Technique	Process	Advantages	Limitations	Applications
Inkjet-based	Droplet-On-Demand technique. Involves one of the techniques mentioned below (6) to dispense droplets onto a collection platform to allow build up of layers in the z direction and eventual construction of a 3D structure (5).	Contactless printing. Allows for modulation of size, position, and deposition rate of droplets. High spatial resolution (38). High cell viability (80-90%) (5).	Cannot use high viscosity materials. Mainly used for printing small scaffolds (38).	in situ bioprinting of skin (60) Blood vessels (35) Human dermal fibroblast (5) Bone and cartilage constructs (5)
	Peizo-assisted			Glia and retinal ganglion cells (36).
	Thermal-assisted		Cellular viability is affected by heat application (36). Nozzle clogging (36).	
Pressure-assisted	Involves the use of plastic or glass cartridge filled with selected bioinks/ biomaterials, ejected in the form of a filament through a nozzle or a needle (36).	Allows dispensing of different combinations of cells and biomaterials (36).	Low resolution. Improving resolution requires decreasing nozzle diameter which results and low cell viability (36).	Cells such as murine pre-osteoblasts, human mesenchymal stem cells, endothelial cells, and osteogenic progenitors (6).

Laser-assisted	Involves a tri-layered system of an energy-absorbing layer, a donor layer and a bioink layer (5). Application of a laser beam to desired sites of energy absorbing layer results in vaporization of corresponding locations of donor layer underneath, leading to the formation of a high-pressure bubble at the interface. This results in impelling of bioink, leading to a droplet falling onto the platform (5).	Nozzle free and so no clogging. Can utilise bioinks of relatively higher viscosity. Allows manipulation of single cells. Allows precise control of position of cell droplets. Fast bioprinting speed (38).	Although resolution is very high, it is dependant on multiple factors such as viscosity of bioinks, speed of laser printing, etc. Laser-induced cellular death during the process leads to low ultimate viability (38).	Human dermal fibroblasts, Graftskin skin substitutes (6). Cornea (49) Bovine pulmonary artery endothelial cells, breast cancer cells, mural neural stem cells (6).

Stereolithography	Utilises photo-polymerisation to solidify bioinks in a layer-by-layer fashion along the z-axis, resulting in formation of complex 3D structures from 2D pattern of interest (5).	First used in reconstructive head surgery to produce accurate models of the cranium (5). Relatively higher bioprinting speed (5). No shear stress is applied to the cells (5). High cellular viability (5). High resolution (5). High Fabrication Accuracy (6).	The liquid used must be transparent with minimum scattering of light (5). Only certain densities of bioinks can be used (5). Unavailability of biocompatible and biodegradable polymers. An inability to completely remove the supporting structure and to form horizontal gradient in the constructs (6).	Alveoli (31) Bone tissue (35)

Extrusion bioprinting	Continuous extrusion of bioink from the nozzle tip (38) driven by three types of systems: pneumatic, piston and screw. The pneumatic system dispenses bioink using compressed gases, piston and screw systems use mechanical forces without gases, dispensing bioink through a pump (13).	High deposition and printing speed (9). Allows bioprinting of a wide range of bioinks with high cellular density, and of anatomically correct porous constructs (9). Printed scaffolds show good structural integrity (38). Fast printing speed (14). Can produce large cell-laden constructs in a controllable manner (14).	Biomaterials need to have high elastic modulus and an appropriate loss modulus. The consistency of the biomaterial should be fluid-like so it can be extruded through the nozzle. Extrusions must be strong so that shape can be maintained, both during and after the process. Relatively low printing resolution. Stress-induced cellular distortion. Low cellular viability (38).	Bone (19) Cartilage (21) Cardiac tissue (20) Nervous tissue (microextrusion bioprinting) (29) Blood vessels (35) Liver (43) Pancreas (47) Cornea (48) Skeletal muscle (35) Hepatocytes (9) Lung tissue analogues (9) Renal organoids (39)

NARRATIVE REVIEW
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Interpreting the Effects of the COVID-19 Pandemic: Bridging Psychological and Sociological Perspectives

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ABSTRACT

Recently, sociologists and psychologists have been investigating the implications of the COVID-19 pandemic, yet much of the social science literature regarding COVID-19 remains partial towards either the sociological or psychological perspective. To mitigate the effects of stigma and guilt, a holistic perspective that integrates sociological and psychological viewpoints needs development.

The purpose of this article is to synthesize evidence on the social and psychological implications of the COVID-19 pandemic. In this context, the author focuses on two key themes, stigma and guilt. The concept of guilt is emphasized by the psychological literature, while, on the other hand, the concept of stigma exists both in sociology and psychology, but tends towards sociological interpretations given its historical origin. Overall, the presence of stigma and excessive guilt are associated with decreased social compliance and increased mortality due to the COVID-19 pandemic.

The author argues that social practices that focus on inclusiveness and preparedness towards mitigating the effects of stigma and guilt—while also complying with public health measures—are crucial for social compliance and increasing societal well-being.

KEYWORDS
COVID-19, Medical Sociology, Social-Psychology, Guilt, Stigma, Pandemic

1 | INTRODUCTION

The most significant global health challenge in recent time has been the novel coronavirus (SARS-CoV-2) outbreak, which was first identified in Wuhan, China, in December 2019 (COVID-19). (1) By March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic, with cases reaching 118,000 in over 110 countries. (2) Speaking of the severity of COVID-19 on March 11, WHO Director-General

Dr. Tedros Adhanom Ghebreyesus said:

> *"Pandemic is not a word to use lightly or carelessly. It is a word that, if misused, can cause unreasonable fear, or unjustified acceptance that the fight is over, leading to unnecessary suffering and death...I have said from the beginning that countries must take a whole-of-government, whole-of-society approach, built around a comprehensive strategy to prevent infections, save lives and minimize impact." (3)*

Dr. Ghebreyesus argues that the COVID-19 pandemic necessitates a thorough, holistic, and societal approach to control and surmount its negative effects. By October 2020, Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, likened the social and public health crisis caused by COVID-19 to the Spanish Flu of 1918, among the worst in history, underlining that "it has devastated the whole world." (4) The impact of this highly contagious disease has been cataclysmic: hospitals have overflowed and lockdowns have been imposed in over 90 countries. (5) COVID-19 has not only caused a public health burden but has also led to social and economic disruptions as well as environmental challenges. The highly contagious nature of COVID-19 led to a collective social effort to mitigate its effects beyond so-called "social distancing." (6) For example, many schools shifted to online/remote instruction, workplaces were adapted to promote distancing efforts and online meetings, travel decreased significantly, and public spaces and restaurants closed down permanently. In the early stages of the pandemic, the global economy became destabilized and the economic impacts of the pandemic were unevenly distributed among the world's population. Recent research has shown that COVID-19 has disproportionately affected different socioeconomic groups within the United States. The lowest socioeconomic groups suffered from higher incidence and mortality rates compared to higher socioeconomic groups. (7) The multitude of factors has led commentators to label this pandemic a period of "new reality." (8)

Within the realm of this "new reality," COVID-19 has had specific consequences for the way in which individuals interact with one another. Due to its highly contagious nature, the disease has altered social interactions in important and often uneven ways especially between different groups in the population. Physical-distancing and the risk of contracting the virus has led to increased social isolation along with psychological unease and fear fueled by negative emotions. (9) Consequently, researchers have been investigating the disease's psychological and social implications. Yet, much of the social science literature remains partial towards one perspective over the other, despite having the common aim to elucidate causal factors underlying the social and psychological implications of the disease. To date, much of the medical literature has been interested in psychological, physiological, and public health consequences of the disease, whereas sociological studies have evaluated the impacts of COVID-19 on society at large and along specific lines of community, politics, and socioeconomic status. In contrast, the primary purpose of this article is to bridge the gap between psychological and sociological perspectives, providing a more comprehensive understanding of the social and psychological implications of the COVID-19 pandemic. This paper focuses on two major themes: guilt and stigma, reviewing them within the context of the COVID-19 pandemic. The social construction of stigma and guilt will be discussed and social-psychological implications on individuals will be depicted using both scholarly literature and news articles.

2 | COVID-19, GUILT AND STIGMA: DEVELOPING A SOCIAL-PSYCHOLOGICAL READING

The concepts of guilt and stigma have been extensively explored in the fields of psychology and sociology. As psychologists June Price Tangney and Kurt W. Fischer have defined it, "guilt is a form of self-conscious emotion that influences our behavioral decisions." (10)

Guilt is the emotion by which individuals reflect and feel distress for their acts. Conversely, the notion of stigma, most famously elaborated by sociologist Erving Goffman, is "an attribute that is deeply discrediting." (11) Goffman differentiates these two terms, indicating the highly social dimension of stigma. Stigmas arise due to relational factors, such as interpersonal interaction or lack thereof. In more recent literature, guilt has mostly been explored through a psychological lens whereas stigma has remained largely within the realm of sociology. Therefore, it is important to highlight the ways in which both guilt and stigma are related through social interaction as well as emotions and psychology. This has been recognized by social psychology scholars like Roy Baumeister et al., who, in 1994, asserted that "guilt is a phenomenon that happens between people as much as it happens inside them." (12) Similarly, stigma has been linked to the concept of deviance, which is a consequence of the responses of others to behavior that breaks social rules. Here it is important to state that deviance is not solely a behavioral quality, but it stems from the interaction between society and the individual committing the act. (13) According to Edward E. Jones et al. (1984), the process of stigmatization is a building block for the social construction of deviance: "it is the essence of the stigmatizing process that a label marking the deviant is applied, and this marking process typically has devastating consequences for emotions, thought, and behavior." (14) This close link between stigmatization and deviance is crucial in analyzing social structure during the COVID-19 pandemic, as mitigating the effects of the pandemic is heavily reliant on either social compliance with regulations or deviation from such stipulations for any number of ideological, political, or other reasons.

The complex processes surrounding guilt, stigma, and deviance inform our perspectives on pandemics and epidemics. For instance, Erving Goffman's dramaturgical theory of social interaction offers useful insight on the sociology of pandemics and epidemics as both lead to an inevitable alteration of social life. Within Goffman's dramaturgical framework, one views social life as a theatrical performance in which we are all actors on metaphorical stages with scripts, roles, costumes, and sets. (15)

But how might this perspective be useful in analyzing the implications of epidemics? In Charles Rosenberg's 1989 paper, "What is an epidemic?", he defines epidemics as a social phenomenon that take on a dramaturgical form: "Epidemics start at a moment in time, proceed on a stage limited in space and duration, follow a plot line of increasing and revelatory tension, move to a crisis of individual and collective character, then drift toward closure." (16) Within this perspective of epidemics and pandemics, the main antagonist is the disease itself. Similarly, what distinguishes a tragic character from a non-tragic one is the state of being infected or not, which allows for the proliferation of social stigma against infected individuals. Thus, it is of utmost importance for social scientists to elucidate the impact of guilt and stigmatization to mitigate the negative societal and psychological consequences of pandemics like COVID-19.

It is also important to consider medical perspectives and more contemporary sociological viewpoints. The diagnosis of COVID-19 evokes worry for possible transmission to a family member, affects work responsibilities, and can promote a pessimistic outlook on the future. (17) In addition to physical suffering, the disease itself will affect one's social-self and social relations. This recalls Susan Sontag's statement in *Illness as Metaphor*: "Etymologically, patient means sufferer. It is not suffering as such that is most deeply feared but suffering that degrades." (18) Therefore, a COVID-19 diagnosis itself is a social and mental burden as much as it is a physical burden. The duality of being sick and being a carrier of the disease complicates our social interactions, which is figuratively depicted in figure 1, providing a concrete analogy to the restriction of intertwined social ties.

2.1 | Stigma during COVID-19: *The Self* as a Victim or as a Threat?

2.1.1 | Social construction of stigma during COVID-19

Pandemics are biosocial phenomena pertaining to the infectious nature of diseases and the requirement of hu-

FIGURE 1 The intertwined ties of social interaction are "closed" due to the COVID-19 pandemic. This image was taken in Huntington Beach, CA., which has been a hotbed of contention around the virus in America in 2020/1. Image © Brian F. O'Neill, used with permission.

man interaction for transmission. Due to the social nature of pandemics, stigma and the negative association attached to infected individuals has led to decreased cooperation with public health guidelines. For example, during the COVID-19 pandemic, fears of being stigmatized led to increased delays in seeking medical care. (19) The fear of being discriminated against or the fear of being held responsible for transmitting the disease may cause an individual to fear testing positive, leading to delays in seeking medical care and decreased compliance with public health regulations.

COVID-19 has caused multiple societal impacts, including, but not limited to, increased social inequalities, marginalization, and xenophobia. (20-22) Additionally, current border restriction policies have to potential to amplify support for anti-immigration policies. (23) The sudden shift towards remote work also poses a challenge for communities of lower socioeconomic status. Higher socioeconomic status is correlated with greater opportunities for remote work, whereas individuals in lower socioeconomic classes are less likely to be involved in jobs performed remotely. (24) This exposes individuals of lower socioeconomic status to a higher likelihood of becoming infected, thus further stigmatizing poorer individuals. In fact, the stigma associated with transmitting the virus led to new social hierarchies in India. (25) During the pandemic, healthcare workers have been the victims of stigmatization, which has even led to harassment and violence. (26-29) Therefore, the perception of risk due to transmission, social roles, and social determinants of health such as access to healthcare, income inequality, culture, and religion, has played a dominant role in the stigmatization of certain communities, leading to increased mortality and transmission of the virus. (30) As in figure 2, where the "sticker" is analogous to the labeling process that leads to stigmatization and the subsequent societal fear emerging from it, the COVID-19 pandemic has generated a climate of societal stigma. To quote the director-general of the WHO, Dr. Tedros Adhanom Ghebreyesus, "Our greatest enemy right now is not the coronavirus itself. It's fear, rumours and stigma." (31)

FIGURE 2 "Fear is the Virus" This image was taken in Huntington Beach, CA., which has been a hotbed of contention around the virus in America in 2020/1. Image © Brian F. O'Neill, used with permission.

2.2 | Stigma and mental health

In light of the COVID-19 pandemic, increased isolation, financial insecurity, limitations to personal freedom, and the highly contagious nature of SARS-CoV-2 have caused detrimental effects on the mental health of individuals. (32) The psychological impacts of quarantine have been reported to range from post-traumatic stress to confusion and anger, amplified by fear, misinformation, and stigma. (33)

The literature has reported that prevalent anti-Asian stigma in the context of COVID-19 could induce anxiety and depression among the Asian community and lead to adverse mental health outcomes. (34) In a study by Charissa Cheah et al., 50.9% of 543 Chinese American parents and 50.2% of their 230 children experienced at least one in-person incident of COVID-19 related direct racial discrimination. Those higher levels of racial discrimination were associated with poorer mental health. (35)

Further, in a review by Giorgi et al., negative mental health effects in the workplace, associated with depression, anxiety, post-traumatic stress disorder (PTSD), and sleep disorders, were more commonly expected among frontline workers and healthcare workers who are in continuous contact with the public. (36) There have even been reports of doctors in India being evicted from their homes amid fears linked to the coronavirus (26,37,38). Clinicians have also been reluctant to share psychological distress, an attitude that has further deteriorated the mental health of healthcare workers. (39)

Due to the fear, isolation, stigmatization, and financial uncertainty surrounding COVID-19, suicide rates have increased across various populations, including the elderly, students, and healthcare professionals. (40) To mitigate the negative mental health consequences of stigma related to the pandemic, researchers have suggested early-preparedness for mental health services, strengthening social cohesion, eliminating false information, increasing general awareness of the disease, and wording sensitively when referring to individuals affected by COVID-19 to prevent discrimination against them. (41-43) Emphasizing and supporting initiatives that aim to address mental health issues during the pandemic is crucial, especially considering that the impact of psychiatric disorders have the potential to persist even following the eradication of the SARS-CoV-2 virus. (44)

2.3 | Guilt and COVID-19

2.3.1 | Collective guilt and social groups during COVID-19

As psychologist Paul Gilbert defines it, “Guilt is rooted in the worry for the well-being of others, such that the distress experiences of others matter.” (45) Gilbert’s notion of guilt has intellectual origins in psychoanalysis. According to Freud, the fear of loss of love from authority figures during childhood, such as parents, is the primitive sense of guilt, which transitions into an internal authoritative voice (superego) during adulthood and judges one’s own acts, rendering guilt to be defined as “superego anxiety.” (46) Similarly, Paul D. MacLean and psychologist Nancy Eisenberg suggest that the origin of guilt often stems from early childhood, when the self-awareness of being a source of distress in others during social interaction leads to the subsequent worry that arises from this realization. (45,47,48) Collectively, the construction of guilt occurs through social interaction and acknowledgment of the “other,” where the latter is a natural consequence of the former.

Émile Durkheim’s notion of “social solidarity,” pertaining to the relationship between the individual and society, depicts the social cohesion that establishes societal order and stability. Social solidarity is further divided into two main types: where *mechanical solidarity* establishes social cohesion through resemblances in values and beliefs, *organic solidarity* is established in more advanced societies through the division of labor. Durkheim also proposes that “collective consciousness” is a unifying force that brings individuals around centrally shared ideas, beliefs, attitudes, and norms. (49) These are the central themes of the formation of collective behavior and collective emotions. (50) The individual awareness of one another’s emotional reactions to-

wards specific events creates a common social identity. For instance, sociology scholars Christian von Scheve and Sven Ismer depict how protest marches exemplify individuals coming together in mutual dissatisfaction, leading to increased awareness of shared emotions and beliefs. This collective awareness ultimately forms a social identity within the group. (51)

The notions of social solidarity and collective consciousness have a bearing on our conceptualization of guilt. For instance, the notion of "collective guilt" arises through the perception that one's group is harming or manipulating another. (52) During the COVID-19 pandemic, we were all responsible for following governmental guidelines to mitigate the transmission of SARS-CoV-2. However, certain groups have disobeyed these guidelines for personal reasons, such as spring break vacation. (53) Moreover, it has been shown that the US counties that voted for Donald Trump (Republican) over Hillary Clinton (Democrat) displayed 14% less social distancing between the dates of March 2020 and May 2020. The authors of this study, Anton Gollwitzer et al., have suggested that *political partisanship* was the key factor linked to social distancing, among other factors such as median income, race, and population density. (54) Therefore, although collective guilt may arise from the subsequent increase in transmission and mortality due to actions of a certain group, mechanical solidarity can overcome it. Leading individuals to choose social solidarity over the guilt that can be sensed when the recognition of the risks posed by COVID-19 would be akin to asking someone to effectively break their extant social ties. Indeed, this phenomenon, coined as *cognitive constraint* by sociologist Craig Rawlings (2020), can occur when attitudes and sentiment relations are unaligned or when social influence can lead us to adjust our attitudes to be more in line with the group's attitude system. *Cognitive constraint* has been elaborated in other case studies of social networks to emphasize how network structure and characteristics inform the way in which people think and feel beyond more atomized theories of the individual. (55)

Aside from protecting one another through social distancing, social media has also served as an important tool for increasing awareness, improving cooperation for the benefit of society, and protecting one another. Conversely, however, sharing *misinformation* can lead to adverse outcomes even if done unintentionally. The sharing of misinformation can also be contagious as it spreads throughout social networks with a snowball effect. For example, in a study by public health scholars Md Saiful Islam et al., the authors provide evidence linking the death of 800 people and the hospitalization of another 5876 to the proliferation of a rumor claiming that concentrated alcohol can kill the virus. (56) In a recent study investigating the role of anticipated guilt in the social correction of COVID-19 misinformation, communication and media scholar Yanqing Sun et al. have elucidated that the possible severity of consequences on others stimulated anticipated guilt, which led individuals to take action and correct misinformation. (57) In a separate study investigating guilt and compliance during COVID-19, psychologists Giovanni A. Travaglino and Chanki Moon have shown that self-reporting and compliance are positively correlated with feelings of guilt. (58) Therefore, feelings of collective guilt can also be *prosocial* and lead individuals to report infections and correct misinformation with the potential of harming others.

The collective actions of individuals, as a social determinant for COVID-19 mortality, may be linked to social solidarity and collective guilt. Therefore, to minimize COVID-19 mortality along these parameters, governments should concentrate their efforts on forming social cohesion against the virus and decreasing the spread of misinformation, which would help eliminate the root causes of collective guilt.

2.3.2 | Psychological toll of guilt during the COVID-19 era

While sociologists have investigated guilt during COVID-19 by analyzing governing social beliefs and structures, psychologists have taken a more individuated approach.

During the pandemic, the emergence of "COVID-19 induced guilt" mainly originated from the fear of transmitting the virus to a loved one. Psychiatry scholar

Swapnajeet Sahoo et al. documented cases of COVID-19 patients who dealt with internalized guilt, shame, anger, and stigma. In one case, a 49-year-old village leader from India tested positive for COVID-19 and felt guilty of possibly transmitting the virus to loved ones and other villagers. News of additional infections throughout the village overamplified his feelings of guilt, which eventually led him to present with psychiatric symptoms, such as sleep disorders and anxiety. Moreover, the report suggests that he started blaming his own lack of responsibility and developed a fear of possible stigmatization that could end his political career. Another report depicts a couple whose baby tested positive for SARS-CoV-2 after they had traveled to India. After the male partner's mother was admitted to the intensive care unit (ICU) due to respiratory distress, the male partner felt intense guilt and blamed himself for her infection. In the same paper, the authors report a 23-year-old man who met with a friend from abroad and contracted the virus. After testing positive for COVID-19, the man became worried about his parents, who had pre-existing conditions. The man later called and blamed his friend for infecting him. (59) In another report, a mother committed suicide after fearing that she might infect her daughters, who were scheduled to visit the following day. The mother suffered from depression and an autopsy revealed that she did not have COVID-19 symptoms or a history of having been infected. The woman's suicide was linked to anxiety over coronavirus and her fear of infecting loved ones. (60)

These reports exemplify individual instances of guilt arising from blaming one's own actions for the transmission of the virus. During the pandemic, guilt has proven to serve as a constructive force for social compliance and taking responsibility; however, in most of the cases described above, guilt has taken the form of *maladaptive guilt*, which occurs when one feels responsible for events that occur outside of the individual's control. Moreover, untreated maladaptive guilt has been shown to lead to mental health disorders such as depression, PTSD, substance abuse, and suicidal ideation. (61)

Similar to maladaptive guilt, patient anxiety is linked with the development of survivor's guilt. (62) Survivor's guilt refers to the discomfort arising from having survived a life-threatening situation when others have not. Survivor's guilt has also had adverse mental health implications during the COVID-19 pandemic. (63)

In addition, feelings of guilt have been reported among healthcare workers. For example, David B. Reuben, M.D., reported "sideline guilt," which he experienced during the pandemic while working as a physician. In his case, he was not required to schedule in-person consults with patients infected with the virus. Yet, media coverage of healthcare workers showing "hand-to-hand combat" on the frontlines coupled with the gratitude shown to him by his patients for his presumed efforts led to "sideline guilt." This type of guilt is misleading because one might think that they are not contributing enough effort in combating the virus because they are on the "sidelines" of the healthcare response to COVID-19. (64)

2.3.3 | Recommendations to prevent stigma and guilt in the general public

From a psychological perspective, negative outcomes of stigmatization and guilt can be decreased through cognitive behavioral therapy, mindfulness-based therapy, and compassion-focused therapy. (61, 65) From a sociological perspective, a social structure that strengthens social support and resilience among communities is crucial for fighting stigma and guilt. For the development of social resilience, governments, physicians, and scientists should combat misinformation not only from a scientific perspective but also from a perspective that aims to eliminate the effects of stigma and guilt. In parallel, creating online support groups can be done by means of telephone helplines that connect individuals with volunteers or healthcare professionals, as well as providing mental health support by telemedicine. (66) In addition, peer-support systems along with increasing awareness of mental health difficulties in healthcare settings should be implemented to support healthcare workers, reduce burnout, and facilitate deeper community-centered engagements. (65) Therefore, multi-faceted approaches that bridge sociological and psychological approaches

with medicine will build social consciousness in the community to actively reduce the effects of stigma and guilt that arose during the pandemic.

3 | CONCLUSION

From a sociological viewpoint, stigmatization and the labelling of infected COVID-19 individuals can lead members of society to fear potential forms of discrimination that result, not from illness per se, but the way that others perceive COVID-19. This stigmatization has had several important consequences, including delayed care-seeking and diagnosis, which posed barriers to compliance with public health guidelines and further affected members of the society in uneven ways.

The psychological effects of isolation have also been varied. Misinformation, combined with stigma, have amplified feelings of anxiety, post-traumatic stress, confusion, and anger, particularly in some ethnic groups such as the Asian community. Front-line workers became particularly susceptible to stigma-induced stress-related disorders, which were compounded by over-work, long hours, and a lack of adequate medical care and equipment.

The literature highlights how various forms of guilt have played a role during the COVID-19 pandemic. It can be prosocial and lead individuals to report infections and counter misinformation, while in other cases it has led to an increased number of psychological disorders.

By synthesizing evidence from sociological and psychological viewpoints and elucidating the role of "stigma" and "guilt" during the pandemic, this paper proposes that— while complying with public health guidelines— healthcare providers, governments, and institutions need to continue to focus on inclusiveness, social cohesion, elimination of misinformation, and preparedness towards mitigating the effects of stigma and guilt for social compliance in healthcare settings.

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SCOPING REVIEW
McGill Journal of Medicine

Applied Theatre and Drama in Undergraduate Medical Education: A Scoping Review

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ABSTRACT

Background: Thematic arts have been integrated throughout various undergraduate medical education programs to improve students' clinical skills, knowledge, and behaviours to train clinically competent physicians. Applied theatre and drama use theatrical performances and exercises respectively to guide education. Several medical schools across Canada and the United States have incorporated applied theatre and drama within their curriculums, but there is currently no compilation of these initiatives.

Methods: Using Arksey and O'Malley's methodological framework for scoping reviews, the two authors searched journal databases for articles pertaining to theatre or drama activities being used in undergraduate medical education in Canada and the United States. Search terms revolved around applied theatre and undergraduate medical education. Twenty articles were read in full, 14 were included in this review. The articles were subjected to content analysis to understand how the studies connected with the CanMEDS framework, allowing to understand the impacts and merits of applied theatre and drama in undergraduate medical education.

Results: Content analyses generated three categories for how theatre and drama can help medical faculties improve their students' communication skills, integrate creative medical learning, and aid professional development. These three categories touched upon all seven aspects of the CanMEDS framework, indicating the value of drama being included in the current framework for medical education.

Conclusion: This scoping review illustrates the intersections between thematic arts and undergraduate medical education by highlighting how applied theatre or drama activities connect to the entire CanMEDS framework. This review informs current theatre and drama initiatives led by medical faculty aiming to develop their undergraduate medical curricula.

KEYWORDS

Applied theatre, Applied drama, Undergraduate medical education

1 | INTRODUCTION

Experiential education allows students to deepen their learning by directly practicing their new knowledge. For medical students, experiential education encourages them to reflect and practice different clinical scenarios they will encounter as a physician. (1,2) Experiential learning in medical curricula is often centred around simulation-based learning and clinical skills training. (1) Overall, experiential education has learners consolidate their learning and test their new knowledge or skillsets in a consequence-free space; helping to develop their critical thinking skills. Ultimately, this should enable them to make good clinical decisions and provide the best care for their patients.

Applied theatre is the use of a theatrical performance, such as having students watch a play, as an experiential educational tool to promote change. (3,4) Relatedly, applied drama refers to learners participating in drama games such as improvisation or role-playing exercises for educational purposes; however, it is important to note that the terms drama and theatre are often used interchangeably in the literature. (4) A debrief commonly follows applied theatre or drama exercises so participants can reflect on how the exercises connect to their previous and new knowledge or experiences. (5,6)

Previous literature demonstrates the positive emotional and professional benefits of applied theatre in medical education. (7,8) Due to the diversity of the field, various medical institutions have taken unique approaches to integrating theatre within their curricula. For example, the University of California in Los Angeles developed an educational initiative that explores palliative care through Wit, a play sharing the final moments of Dr. Vivian Bearing who suffered from metastatic ovarian cancer. The performance of Wit is followed by a discussion regarding the play's themes. (9) The play Wit has also been used for students to explore compassion and empathy in an introductory clinical practice course at the University of Arkansas for Medical Sciences. (10) However, currently there is no compilation of applied drama programs to understand the overall educational and personal impacts of theatre for undergraduate medical trainees. The aim of this review is to gain a broad understanding of how drama and theatre are currently being used at different medical schools.

2 | METHODS

To 'set the stage' of the current literature surrounding applied theatre and undergraduate medical education, a scoping review was conducted A scoping review provided the opportunity to identify and evaluate the fairly unexplored literature pertaining to applied theatre in undergraduate medical education. (11–13) The five steps outlined by Arksey and O'Malley were consulted to help researchers collect, organize, and analyze the data from the various studies found in this literature search. (11)

2.1 | Ethics

Ethics approval was not required for this research, as only existing published literature was reviewed.

2.2 | Stage One: Identifying the Research Question

The research question for this project was: *how have applied theatre and drama been used as educational initiatives in medical schools across Canada and the United States (USA)?* This review was directed at Canadian literature, as the intent was for Canadian faculty to understand how theatre is currently being incorporated into schools with similar learning objectives, resources, and student populations; enabling them to upon these initiatives to include theatre or drama in their medical curricula. Given the close contact and frequent collaborations with the USA, publications from American institutions were also included.

2.3 | Stage Two: Identifying Relevant Studies

Various science and humanities databases were consulted to get a wide perspective of the current work sur-

rounding theatre activities for medical students. These databases were: PubMed, OVID, Web of Science, Education Resources Information Center, and Applied Social Sciences Index and Abstracts. A search strategy was developed in collaboration with the entire research team; a librarian was consulted for feedback on the search criteria. The search terms employed across all databases are listed in Figure 1. Only peer-reviewed articles were included to help ensure methodological oversight of the selected journal articles.

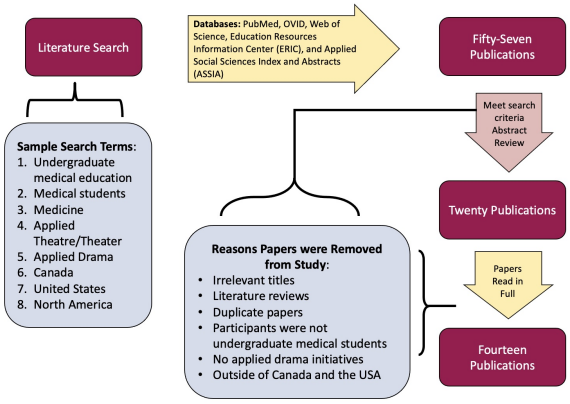

FIGURE 1 A Summary of the Methods in this Scoping Review.

2.4 | Stage Three: Study Selection

Strict inclusion criteria were employed to ensure the applicability of all included articles. Only studies that specifically discussed an applied theatre or drama initiative, involved undergraduate medical learners, and had connections to Canada and the USA were included in this review; all other research was excluded from this study. As the field of applied theatre and drama in medical education is small, no limits were placed on study publication dates. Only studies published in the research team's first language were included to ensure appropriately interpretation of the studies.

The search results were then filtered based on their connections to the research question and if they clearly met the search criteria from their titles and abstracts. Duplicate articles were removed by BKJ. Relevant articles were then read in full by both researchers (BKJ and HJ) to ensure they met all aspects of the search criteria and the research question; the final selected papers were then analyzed (Figure 1).

2.5 | Stage Four: Charting the Data

Data from the papers was extracted in a table that listed the: study title, year of publication, a brief study description, the study location, and respective citation to organize all papers (Table 1). All included articles were published in peer-reviewed journals.

2.6 | Stage Five: Collating, Summarizing, and Reporting the Results

To qualitatively analyze the data from the included papers, conventional content analysis was chosen to provide in-depth perspectives on the authors' experiences and opinions of drama in undergraduate medical education. Given the variations on how applied theatre can be used as educational methods, inductive content analysis provided a high degree of flexibility for researchers to collate the categories and nuances from the different studies. (14,15) The included papers were read once in full before any coding occurred to jot field notes in order to start understanding their described phenomena. After the first review, initial coding was done by BKJ, selecting clear descriptions, comments, and analogies from the papers to minimize the risk of data misinterpretation. All initial codes were then consulted by the entire research team to ensure that they reflected the authors' messages and data. The codes were also organized to see how they connected to the seven factors of the CanMEDS framework: communicator, collaborator, leader, health advocate, scholar, professional, and medical expert. (16) The CanMEDS framework was chosen to guide qualitative analyses, as it is the "most widely accepted and applied physician competency framework in the world." (16)

The data codes were then refined and grouped to generate the overarching categories of this review. The

three categories were reviewed again by the entire research team (BKJ and HJ) to ensure they accurately reflected the study descriptions on how applied theatre facilitates learning for medical students, landing on the final categories of this scoping review. All coding was done with NVivo12 software.

3 | RESULTS

Throughout the databases, 57 search results were filtered based on their relevance to the research question. The search criteria were run three times in January 2019, March 2020, and June 2021. Twenty relevant articles were read in full by the entire research team. In total, 14 publications were included in this scoping review (Figure 1). The publication dates ranged from 2003 to 2018, with the majority of articles (n=8) being published after 2010. Two articles were from Canada, seven were from the USA, and five papers were either spread throughout Canada and the USA or had affiliations with these two countries. The study populations varied in size - some initiatives were located at one university while larger studies were composed of conference workshops or collaborations between multiple medical schools (Figure 1).

3.1 | Types of Applied Theatre and Drama Initiatives

While each theatrical initiative was different, they can be summarized into two groups: 1) applied theatre followed by educational activities (n=6) and 2) applied drama exercises (n=8). Authors described drama or theatre activities they had created, or how educators integrated previously established material, like the play Wit (9,10), into their medical curricula. These articles shared student and faculty experiences and learner receptions of their theatre initiatives through student reflections/sharing of their experiences (10,17,18), course evaluations (5,6,17,19), student and faculty feedback (20,21), and group discussions (9,22,23). Some authors shared how they used surveys without further description of items (10,24–26), others were specific in sharing that they used a combination of quantitative and qualitative survey questions (24–26), and some only included quantitative questions. (10) The utility and benefit of applied theatre and drama in undergraduate medical education were illustrated by three categories of communication, creative medical learning, and professional development.

3.2 | Communication

Communication refers to the verbal and non-verbal exchanges of information from physicians to patients as well as the collaboration between healthcare providers. (16) Overall, communication was referenced in all papers (n=14), highlighting the extensive role it plays in medicine. Generally, drama allowed medical students to focus on expressing their ideas and experiences to improve their communication skills (Table 1). Specifically, Hoffman, Utley, and Ciccarone created an elective where first year medical students used improvisation to understand their personal perceptions and interactions with each other which helped them develop "strong communication skills… [to become] an effective health provider." (6) Improvisational theatre also improved medical students' storytelling abilities, enhancing the clarity of their ideas in clinical presentations. (18–20,24) Additionally, role-playing exercises involved students playing different parts in a scene so they could practice various interactions with patients and colleagues. (20,23,25) These drama activities were well received by students; for example, Hammer et al. stated that students perceived their listening and communication skills to be stronger as a result of drama being included in the curriculum. (24) Overall, drama helped teach learners how to deconstruct a conversation or improved their articulation abilities to clearly convey relevant clinical information.

Non-verbal communication skills were also discussed in the articles. Examples of non-verbal communication methods mentioned throughout the studies included, body language, gestures, eye contact, non-verbal expressions, and personal awareness. (5,9,17,24) Drama exercises targeted towards non-verbal communication

skills allowed learners to further understand how to read others' body language, the implications of their behaviour, and how they could improve their own non-verbal interactions. The play Wit illustrated the humanistic sides of palliative care. Notably, medical students saw how they needed to non-verbally communicate to emotionally support their patients; something that is challenging to teach using traditional didactic methods as they often overlook the complexities of coping with illness. (9) Watching a play or participating in role playing exercises allowed students to experience their patients' fears and challenges, gaining a deeper understanding of illness and how to better support their future patients. (9,10,19) Drama workshops centred around acknowledging the senses helped students improve their awareness of others' emotions to provide more empathetic care. (5)

Altogether, applied drama and theatre provided learners with opportunities to unpack both verbal and non-verbal communication skills to improve their interprofessional dynamics between colleagues and patients. It is important to note that throughout the papers, there was more emphasis on teaching verbal communication skills in comparison to non-verbal skills.

3.3 | Creative Medical Learning

Theatre provided students with unique ways to emotionally connect with their medical learning (Table 1). Watching various productions of real patient stories brought to life for students the trials and tribulations patients experience with illnesses. (17) Comparably, Wit was well received by 95% of students, with many stating that they were "emotionally moved" by the performance and that it helped them further understand compassion and empathy (humanistic medicine) as well as palliative care. (9) By watching a play, students were able to experience realistic difficult patient stories through the safety of a storyline, making it an effective teaching tool to introduce challenging topics. Wit covered the difficult realities surrounding cancer and palliative care. (9) Drama provided learners with the freedom to think critically and divergently by creating an accepting learning environment where students saw that there is not necessarily one correct way to analyze a case or make good clinical decisions as a physician. (21,24,26) Additionally, the immersion students felt within a storyline opened their eyes to different perspectives and how they can connect deeper with their emotions, skills they can carry throughout their medical education and careers. (17,26)

The importance of experiential education in medicine can be summarized by one student's thoughts about how "it is so hard to imagine without experience." (25) These articles shared the importance of students actively participating in class to translate their new medical knowledge and skills into clinical experiences. Some educators did not directly focus their drama exercises on healthcare, but rather encouraged students to make their own connections on the relations between applied drama and medicine. (5,21) Kelly et al. (5) showcased how:

> *Listening attentively in the clapping game generated discussion about how physician can anticipate what one will hear, and jump to conclusions. Touching, as experienced in the human clay exercise and neck examination, prompted conversations about touch as a form of human connection. (5)*

Role-playing was also frequently used for students to embody different characters or personas, often to replicate the patient-physician dynamic. (5,19,20,25) Medical students can often feel intimidated or unsure with how to proceed through challenging clinical scenarios, and playing the role of a clinician allowed learners to practice their clinical counselling skills in the security of drama. Students playing multiple characters were also excellent opportunities for learners to broaden their perspective of a scenario to understand what other 'characters' are feeling. Overall, theatre promotes the "retention and synthesis of new knowledge," which aids students in becoming highly skilled, compassionate, and empathetic clinicians. (20)

3.4 | Personal Development

Personal development refers to a students' ability for self-awareness and ability to improve their potential in both their professional and personal selves. Empathy was one of the most highly discussed skills educators felt was essential for students to be proficient in after medical school. Many teachers turned to theatre to facilitate empathy teachings and discussions for their students (n=9). (5,9,10,18,20,21,23–26) Consistently, drama and theatre exercises encouraged learners to care about a story and its characters. This provided insights to medical students in starting to understand patient-physician relationships, as well as how they could enhance their capacities to support others. (10,21)

Compassion was also widely discussed with respect to encouraging learners to reflect upon recognizing others' pain and how they could help. (10,17,18,23) Experiencing Dr. Bearing's cancer journey in Wit, medical students felt that this play gave them "a strong foundation for delivery of compassionate care in difficult situations" and how the arts can help keep patient stories at the forefront of their undergraduate medical training and future careers. (10) Playback theatre is another form of improvisational theatre that promotes personal development in which an audience member shares a story that is then performed by the actors. Medical students could form "connections with the audience" to more efficiently recognize the reactions and feelings of others as well as reflect on the shared peer stories in Playback Theatre, key aspects of compassionate care. (18)

Introducing theatre to medical students also helped them to understand the importance of establishing a professional-personal balance. Throughout the articles, enjoyment (19,22), stress relief (18,19,22), and wellbeing (22) were all attributed to drama being used in medical education. The joys theatre brought to medical school encouraged students to take breaks from academics, which re-iterated the importance of creating a work-life balance.

Overall, theatre was positively received and it was encouraged to continue using it as part of undergraduate medical education. For example, 95% of Northwestern University Feinberg School of Medicine's students who completed an improvisation class agreed that "studying improv could make me a better doctor" and recommended this course to their peers. (19)

4 | DISCUSSION

The papers included in this scoping review highlight the importance of applied drama and theatre being integrated within three components of the undergraduate medical curriculum: communication, creative medical education, and personal development. Together, these three categories encompass the entire CanMEDS framework to help make students medical experts (Figure 2). (16,27)

Specifically, the category of communication directly connects to the communicator and collaborator traits (Figure 2). (16) Medical students need to have strong verbal communication skills to clearly convey relevant clinical information or to educate their patients on their conditions and respective treatment plans. Applied drama provides students with ample opportunities to practice the skills they will need as a physician such as case addresses, clinical presentations, and navigating the patient-physician dynamic. (20,23,25) Physicians also need strong non-verbal communication skills to fully disclose their intended tone and also to pick-up on subtle non-verbal cues such as posture, tone, or hand gestures from their patients; skills Saldaña, Konos, and Naglie argue can be better taught through theatre in comparison to traditional teaching methods. (28–30) Theatre encourages awareness so trainees can understand how eye contact, body language, and facial expressions emphasize their intended messages and feelings, traits that will help medical students understand "how empathy is experienced and expressed." (31) Finally, drama also permits students to connect or move with their bodies to understand the role their body, movements, and expressions play in communication. (5)

Further, applied drama helps create a safe learning environment where students can view healthcare issues

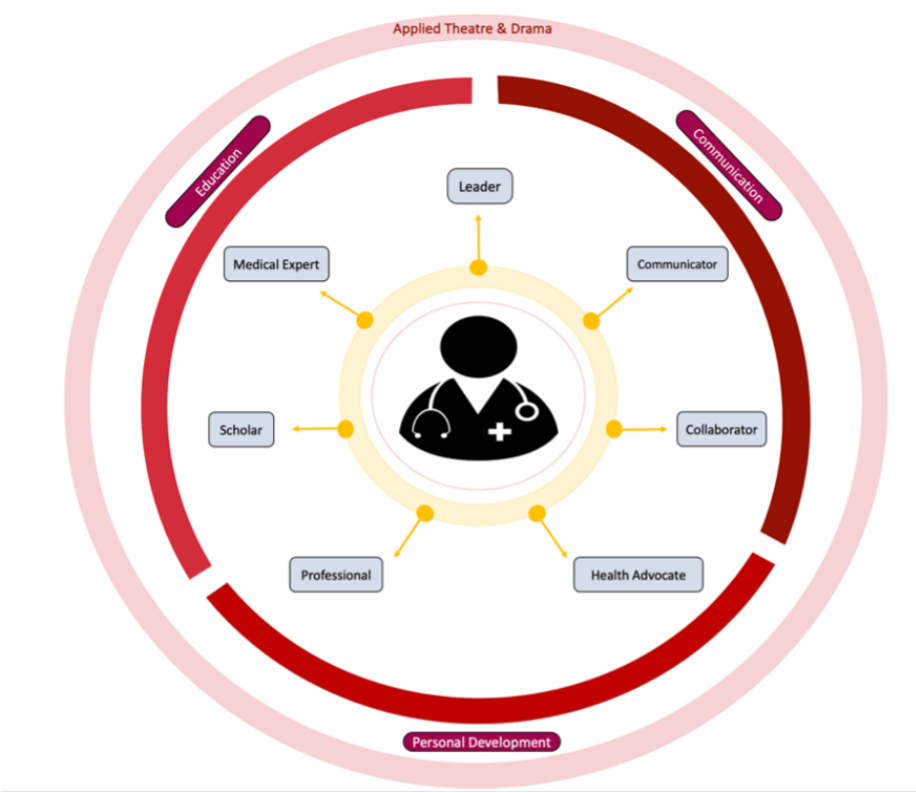

FIGURE 2 The Overarching Parent-Categories and their Relations to the CanMEDS Framework. Image adapted from the CanMEDS Physician Competency Diagram with permission of the Royal College of Physicians and Surgeons of Canada.

through the eyes of an actor, as opposed to an actual clinician or patient. Drama exercises, notably improvisational theatre, also encourage students to take risks, think outside the box, and try new ideas to improve their practice. (32) Medical learners can refine their knowledge and work to become scholars and medical experts by acting out the new concepts they have learned in class. In doing so, they can identify their current strengths and areas of improvement to maximize their study revisions (Figure 2). (16)

The interactive and reflective nature of theatre and drama also encourages personal development in learners. The CanMEDS framework focuses on how physicians are to be healthcare leaders, a trait which connects to strong medical education and communication skills. (16,27) Theatre and drama as experiential education allow students to expand their didactic healthcare knowledge and clinical skills, which they can carry forward in leadership positions (Figure 2). Notably, plays (applied theatre) allow undergraduate medical students to appreciate various perspectives of a scene. This can help them emotionally connect (29) and reflect on these stories, such as how would they feel being in that patient's position or how they would have resolved character conflicts. (9,10,17,26) Consistently showing patients' perspectives and experiences keeps them at the forefront of medical education. Patient stories also illustrate the importance of altruism in healthcare and leadership —something challenging to achieve in traditional course materials because patients can get lost in the facts and statistics that students learn in lectures (Figure 2).

Applied theatre and drama encourage student reflections and a critical consciousness to help learners guide their self-improvements. Debriefing and discussing activities or drawing connections between

drama and medicine helped learners develop critical reflection skills that they can use and continue refining throughout their professional careers. Improvisational theatre also encouraged students to think quickly and translate their thoughts efficiently to help improve medical learners' adaptability for their medical careers. The playful nature of theatre creates a fun and enjoyable learning space that promotes student participation. Partaking in therapeutic activities, like drama, encourages personal wellbeing and promotes health advocacy, therefore providing a potential solution to combatting the major issue of student burnout (Figure 2). (16,33)

Altogether, this paper showcases the various ways drama can help trainees become medical experts (Figure 2). While some Canadian and American medical schools have integrated theatre into their curriculums, overall theatre and drama unfortunately remain underutilized in curricula to facilitate medical learning. Therefore, more considerations for how applied theatre and drama can be integrated into medical education are needed to better educate and support medical students. It is hoped that this review will help undergraduate medical faculty realize the potential and understand how theatre can improve curricula.

5 | LIMITATIONS

Purposefully, the research question for this project was tailored to specifically evaluate current drama and theatre educational initiatives in medical school in Canada and the USA in peer reviewed journals. Therefore, minimal publications (n=14) were included in this review. A lack of literature makes it challenging to thoroughly analyze the depths of how theatre can enhance medical education and may also hinder the generalizability of the results in this scoping review. Another limitation is that this review only included articles in English; this could impede the generalizability of these results to all Canadian universities as some schools are French-English bilingual or only instruct in French.

6 | FUTURE RESEARCH

Given the benefits of applied theatre and drama within undergraduate medical education, additional research to further understand the impacts of theatre in other health professions' education programs, such as post-graduate medical training or nursing, should be carried out. A systematic review on applied theatre is also recommended as a future research project , so as to have a deeper global perspective on how it is being used in undergraduate medical education across the world . Additionally, the study period for the majority of papers in the present review were quite short.; educational theatre initiatives largely took place over an academic year or a semester. Therefore, more research on the long-term influences, such as throughout students' entire medical degree, of applied drama education for medical students is recommended. Additionally, with the difficulties in educating students during the Coronavirus-19 (COVID-19) pandemic, and now the progressive safe return to the classroom, one wonders if or how theatre has been used in medical education in response to COVID-19.

7 | CONCLUSIONS

Applied theatre and drama are unique educational tools that encourage creative medical learning, communication, and personal development for undergraduate medical students. The innovations and flexibilities that drama and theatre provide facilitate a diversity of experiential exercises that overlap with all aspects of the CanMEDS framework. (16) The utility and merit of theatre and drama in medical school should be further explored to improve current curricula so that trainees can provide the best care to their future patients.

ACKNOWLEDGEMENTS

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framework in this work.

CONFLICTS OF INTEREST

We, the authors, declare no conflicts of interest associated with this research.

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Title	Publication Year	Brief Study Description	Location	Citation
End-of-Life Education Using the Dramatic Arts: The *Wit* Educational Initiative	2004	*Wit* was performed for medical students and other healthcare providers for palliative care education. Survey respondents shared how *Wit* helped their palliative care learning. **The Wit Initiative was shared throughout Canada and the USA.*	Author Affiliations: California, USA	Lorenz KA, Steckart MJ, Rosenfeld KE. End-of-life education using the dramatic arts: the Wit educational initiative. Academic Medicine. 2004 May 1;79(5):481-6.
Exploring the Benefits of an Optional Theatre Module on Medical Student Well-Being	2013	A theatre-based module focused on empathy was created for students. These sessions were fun for learners and facilitated relationship building between each other and promoted personal growth.	Alberta, Canada	Nagji A, Brett-MacLean P, Breault L. Exploring the benefits of an optional theatre module on medical student well-being. Teaching and learning in medicine. 2013 Jul 1;25(3):201-6.
Developments: Wit: using drama to teach first-year medical students about empathy and compassion.	2003	*Wit* was included in a module to teach empathy and compassion. *Wit* was performed for students after a pre-play lecture, followed by a discussion with faculty, the cast, and cancer survivors. This initiative emotionally moved students and promoted positive attitude changes in students' empathy skills.	Arkansas, USA	Deloney LA, Graham CJ. Developments: Wit: Using drama to teach first-year medical students about empathy and compassion. Teaching and learning in medicine. 2003 Oct 1;15(4):247-51.
Headspace Theater: An Innovative Method for Experiential Learning of Psychiatric Symptomatology Using Modified Role -Playing and Improvisational Theater Techniques	2007	Headspace theater used role-playing to simulate psychiatric conditions in small groups. This research consulted improvisational drama experts to share their experiences with medical students in addition to a literature review. Headspace theater was positively received by learners to understand the patient experience.	Author Affiliations: Ontario, Canada West Virginia, USA	Ballon BC, Silver I, Fidler D. Headspace theater: an innovative method for experiential learning of psychiatric symptomatology using modified role-playing and improvisational theater techniques. Academic Psychiatry. 2007 Sep 1;31(5):380-7.
Drama to promote non-verbal communication skills	2018	Drama exercises were used to teach and refine non-verbal communication skills for medical students. This workshop allowed participants to have more awareness of non-verbal communication skills to aid with trusting relationship development.	Author Affiliations: Alberta, Canada Colorado, USA Belfast, United Kingdom	Kelly M, Nixon L, Broadfoot K, Hofmeister M, Dornan T. Drama to promote non-verbal communication skills. The clinical teacher. 2018 May 23.
Using Theater to Increase Empathy Training in Medical Students	2012	A drama workshop to help teach communication skills, professionalism, and cultural competency was created. The workshop included various drama games, reflective writing, and images. This curriculum received positive feedback for teaching empathy, although some students struggled to understand the purposes of this workshop.	USA Author Affiliations: California, USA	Reilly JM, Trial J, Piver DE, Schaff PB. Using Theater to Increase Empathy Training in Medical Students. Journal for Learning through the Arts. 2012;8(1):n1.

Perspective: Serious play: teaching medical skills with improvisational theater techniques.	2011	A medical improvisation seminar was offered to medical students to improve their communication and professionalism skills. Students appreciated how the seminar promoted creativity and how they could immerse themselves into the exercises to improve their communication skills.	Illinois, USA	Watson K. Perspective: Serious play: teaching medical skills with improvisational theater techniques. Academic Medicine. 2011 Oct 1;86(10):1260-5.
Use of interactive theater and role play to develop medical students' skills in breaking bad news.	2014	An interactive drama class was centred around improving student skills of breaking bad news to patients. Actors played the patients and a small group of students had to practice breaking bad news to them. Students shared that they appreciated how this session promoted them to reflect up patient-physician communication and that the seminar was valuable.	Author Affiliations: Michigan, USA District of Columbia, USA	Skye EP, Wagenschutz H, Steiger JA, Kumagai AK. Use of interactive theater and role play to develop medical students' skills in breaking bad news. Journal of Cancer Education. 2014 Dec 1;29(4):704-8.
Theatre: An innovative teaching tool integrated into core undergraduate medical curriculum	2013	A verbatim play, *Ed's Story: The Dragon Chronicles* tells the story of a 16-year-old boy who has cancer and unfortunately passed away based on interviews with Ed's loved ones and his journal. Students were required to watch the play and then participate in a discussion. Medical students felt that *Ed's Story* should be mandatory in medical curricula.	Canada Author Affiliations: Nova Scotia, Canada	D'Alessandro PR, Frager G. Theatre: An innovative teaching tool integrated into core undergraduate medical curriculum. Arts & Health. 2014 Sep 2;6(3):191-204.
Playback Theatre as a tool to enhance communication in medical education	2013	Playback Theatre (PT) is improvisational theatre where performers act out real-life stories that the audience shares with them. PT performances were offered to medical students to share their stories and helped learners better communicate their emotions to others.	Texas, USA	Salas R, Steele K, Lin A, Loe C, Gauna L, Jafar-Nejad P. Playback Theatre as a tool to enhance communication in medical education. Medical education online. 2013 Jan 1;18(1):22622.
All the world's a stage: the use of theatrical performance in medical education	2003	Two one-actor plays on the patient experiences of living with AIDs and ovarian cancer were performed for medical students followed by a discussion. These performances helped students understand patient care and the importance of empathy in medicine.	California, USA	Shapiro J, Hunt L. All the world's a stage: the use of theatrical performance in medical education. Medical education. 2003 Oct;37(10):922-7.
Telling the Patient's Story: using theatre training to improve case presentation skills	2011	Drama training was integrated into medical education to help students refine their case presentation skills. The authors commented on the correlation between storytelling and communication skills in medical students.	Minnesota, USA	Hammer RR, Rian JD, Gregory JK, Bostwick JM, Birk CB, Chalfant L, Scanlon PD, Hall-Flavin DK. Telling the patient's story: using theatre training to improve case presentation skills. Medical humanities. 2011 Jun 1;37(1):18-22.

In their own words: presenting the patient's perspective using research-based theatre	2005	The theatrical piece: *In Their Own Words*, was created by playwrights who have experienced illness. This piece was performed for first year medical students. The student's reflections indicated their increased awareness of hearing the patient perspective and the importance of providing patient-centred care.	Iowa, USA	Rosenbaum ME, Ferguson KJ, Herwaldt LA. In their own words: presenting the patient's perspective using research-based theatre. Medical education. 2005 Jun;39(6):622-31.
Improving medical student communication skills through improvisational theatre.	2008	First year medical students completed an elective centred around drama improvisation in medicine. These theatre exercises were centred around how students portray themselves, as well as their perceptions and interactions with others. Students appreciated the elective and its respective debrief to better understand the patient-physician dynamic.	Author Affiliation: California, USA	Hoffman A, Utley B, Ciccarone D. Improving medical student communication skills through improvisational theatre. Medical education. 2008 May;42(5):537.

TABLE 1 A Summary of the Fourteen Papers Included in this Scoping Review.

CASE REPORT

Artist: Claire Chabot

CASE REPORT
McGill Journal of Medicine

Depression and Anxiety as Important Aggravating Factors of Pain in Morton's Neuroma: A Case Report

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ABSTRACT

This report represents a case of Morton's neuroma with episodic severe pain in the forefoot. Initially, the patient was prescribed naproxen 500 mg twice per day, anti-inflammatory topical cream, and massage. In a follow up visit, the patient was still experiencing frequent episodic sharp pain. In a detailed patient interview, it was revealed that she has depression and anxiety and suffers from social isolation, which co-occurred with episodes of severe pain. Therefore, she was referred to a psychologist and a community support group and started practicing body relaxation techniques such as guided imagery and breathing exercises. The new treatment strategy had a major impact on improving her symptoms. This report aims to illustrate that depression and anxiety can be one of the main aggravating factors in conditions that cause episodic pain, as in this case of Morton's neuroma. Removing psychosocial contributors of pain has the potential to decrease the need for more invasive interventions.

LEARNING POINTS

- This study highlights the importance of recognizing psychosocial contributors of pain in a case of Morton's neuroma
- Taking a detailed history is essential to recognize all the potential triggers of pain, even when the disorder has a typical presentation with an identified pathology
- By evaluating and identifying psychosocial contributors, the necessity of painkillers and invasive interventions can subside

KEYWORDS

Morton's neuroma, Pain, Biopsychosocial model

1 | INTRODUCTION

Morton's neuroma is one of the most common causes of forefoot pain. (1) It can develop when the tissues and bursa surrounding an interdigital nerve thicken from chronic pressure and lead to swelling or fibrosis around the vessels and the nerve. (2) The resultant neuropathy is mainly due to irritation of the interdigital nerves close to the plantar aspect of the transverse intermetatarsal ligament during dorsiflexion. (2) Common causes include narrow toe-box footwear, high heels, lipoma, joint dislocations, repetitive trauma, or blunt injury. (3)

Morton's neuroma mostly occurs between the third and fourth metatarsals and pain may radiate to other toes, though occurrences between the second and third metatarsals has also been reported. (4) The most common aggravating factor is walking, especially in tight or high-heeled shoes, and the most common relieving factors are resting and taking off footwear. (2) Numbness and night-time awakening pain can happen, (4) and with prolonged activity, pain can radiate to the calf and other parts of the foot as well. (2) The first-line treatment option is supportive care, such as wearing a wide shoe with soft insoles and a low heel that unloads the pressure on the nerve. (2) Nonsteroidal anti-inflammatory drugs, anti-epileptic medications, and tricyclic antidepressants may also be effective. (2) Injection of anesthetics as a gentle invasive treatment is used as second line. (2) Steroid injection is a short-term effective symptom reliever but may cause side effects, including atrophy of the subcutaneous fat, skin thinning, and even deformity. (2) The effectiveness of surgical interventions remains controversial thus, they are usually reserved for when conservative management has failed for at least several months. (3) The CARE guideline was used to guide this case report. (5)

2 | CASE REPORT

Patient's presenting profile: the patient is a 70-year-old female, admitted to the outpatient department, complaining of sharp and severe episodic pain in the tip of the left second distal phalanx. Subjective history revealed an insidious onset that started around seven years ago with no known history of trauma. Since then, the patient has been changing her footwear regularly, as it alleviates her pain. While she has excruciating pain, she notices warmth and visible bulging of the veins on her foot however, denies any numbness, tingling, or cramps. Over the course of two years, her pain has intensified and the periodic events no longer correlate with activity, which was previously an aggravating factor for pain. Nevertheless, she does mention that long walks bring forth a tingling sensation in the forefoot. In order to alleviate her pain, she has been taking over-the-counter medications, including ibuprofen and topical remedies. Unfortunately, these medications have provided no relief. Furthermore, the patient denies wearing tight shoes, and reports performing a mild level of physical activity (i.e., slow-paced walking). The persistent pain has been distressing her, as she expresses feelings of nervousness and hopelessness.

Past medical history: her past medical history consists of hallux valgus correction surgery done on bilateral feet four years ago, with no post-operation complications. She denies wearing high heels for over 45 years. She also reports taking 20 mg of citalopram daily for mild depression for the past fifteen years. The patient denies diabetes, rheumatic diseases, allergies, kidney, liver dysfunction, recreational drugs, alcohol abuse, and any family history of similar type of pain.

Physical examination: vital signs and body mass index were normal. On inspection, there were no swelling, discoloration, or atrophy at the location of the pain. The shape and color of the nails were normal. There was no warmth, mass, crunching, lump, or clicking. On palpation, save for the second toe, other parts of the left foot had no tenderness. Dorsalis Pedis and Tibialis arteries' pulses, as well as capillary fillings were normal. The dermatomal assessment was symmetrical and unremarkable. The range of motion of the joints were within normal limits. On X-ray, no signs of fracture, injury, or trauma to the second metatarsal and phalanx were visible. On MRI, Morton's neuroma by the second metatarsal was detected by a radiologist (Figure 1). The pa-

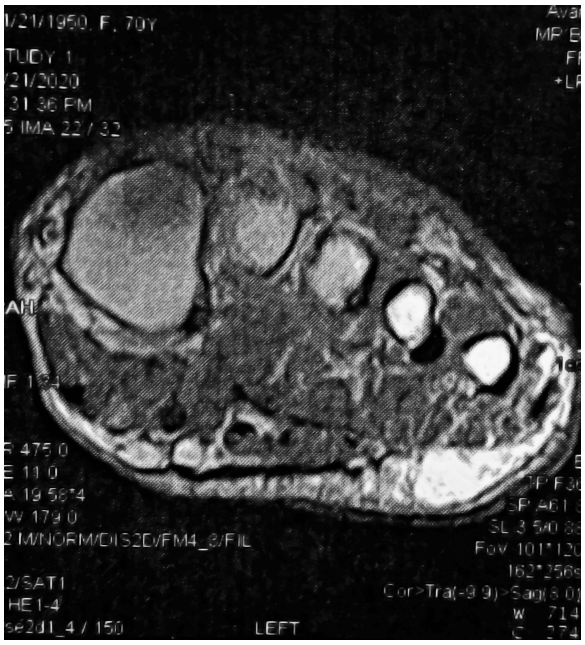

FIGURE 1 MRI scan of the left foot showing Morton's neuroma at the second metatarsal.

tient rated her pain at 8/10 on the numeric pain rating scale (NPRS). A squeeze test was performed by applying pressure on the dorsal and plantar surface of the second distal meta-tarsal. A Morton's test was conducted in which one hand was placed on the medial side of the patient's foot near the metatarsophalangeal joint, and the other hand was placed on the lateral side, and pressure was applied to squeeze the two sides. The results of both tests were positive with the reproduction of the familiar pain. The patient was advised to use topical salicylate ointment and to gently massage the second and third metatarsals by spreading and mobilizing the metatarsal heads. She was also advised to take 500 mg naproxen, a maximum of two tablets daily.

Psychosocial assessment: Three weeks later, the patient still reported the same amount of pain in a follow-up visit. During this visit, a more thorough patient interview including evaluations of social and psychological factors was conducted. The patient revealed that she suffers from social isolation with no family and social support. In addition, the patient indicated that she has been experiencing anxiety in the past two years, which was concurrent with the severe pain onset. She displayed depression and anxiety symptoms, including nervousness, restlessness, agitation, fatigue, sadness, and loss of interest in activities of daily living (ADLs). According to the patient, her mental health also affects her appetite, ADLs, and sleep quality. Her score on the Hospital Anxiety and Depression Scale was 15/21, depicting presence of depression and anxiety.

Analysis: Upon further investigation, it was revealed that her pain exacerbates at times of severe depression and anxiety. In other words, there was a strong correlation between episodes of pain in the forefoot and when she felt extremely sad and anxious. Based on this finding, she was referred to a psychologist for weekly sessions and a community support group to address her social isolation. In the meantime, she started body relaxation techniques such as guided imagery and breathing exercises on a daily basis (at least one or two times per day). These strategies were in addition to the previously prescribed treatments such as specific massage techniques, naproxen, and topical salicylate ointment. After four weeks, in a follow-up visit, her pain level had decreased to 4/10 on the NPRS, which was controllable by taking 500 mg naproxen a day. The patient's mental status improved, and she reported a significant decrease in the frequency of painful forefoot episodes.

3 | DISCUSSION

To the authors' knowledge, this is the first case report of a patient with Morton's neuroma having social and psychological factors as the main triggers of pain. This study highlights the necessity for considering these triggers and working towards removing them to not only reduce the need for pharmacological treatments, but also decrease the necessity of invasive interventions. This finding is in line with the biopsychosocial model of pain, which posits that not only tissue pathology contributes to the experience of pain, but that also social and psychological factors play important roles. (6)

Psychological factors such as depression have been reported as significant predictors of chronic pain following an injury. (7) Uncovering the exact underlying

mechanism of how psychosocial factors could have affected the experience of pain for this patient is beyond the scope of this paper however, we can offer some explanations. Previous research has shown that people with high levels of anxiety are more sensitive to pain, and stress or other negative emotions are associated with lower pain thresholds. (8) In addition, pain shares some common biological mechanisms with depression and anxiety. For instance, various parts of the brain have vital roles in processing both anxiety and pain such as the periaqueductal gray and anterior cingulate cortex, as both regions get activated while feeling either pain or anxiety. (9) Even the severity of pain and psychological disorders are significantly correlated with each other. (10) This overlap of biological mechanisms can also lead to a vicious cycle between pain and psychological disorders, as pain is a risk factor for developing depression and anxiety. (9) Also, neurotransmitters such as glutamate have shown to play essential roles in regulating both mental health and pain. (9) In addition, emotional disorders might affect pain through other health behaviors such as nutrition and sleep. (7) Therefore, clinicians are recommended to screen for depression and anxiety, especially if the patient suffers from severe chronic pain. Focusing on typical causes and triggers may hinder the clinicians' and the patients' awareness that an underlying psychiatric condition may exist and potentially play a significant role. By going beyond the pathophysiology of a disorder, identifying the psychosocial contributors of pain, and implementing these factors into the management strategy, we can decrease the necessity of painkillers and invasive interventions, and optimize individualized care that is evidence-based and comprehensive.

This case report's principal strength is that it provides a clear example of how psychosocial factors can be the main triggers of pain, in this case for a patient with Morton's neuroma. The main limitation is the inability to create a causal link between depression/anxiety and the episodic periods of pain. Further research is required to establish a definite cause and effect relationship. Informed consent was obtained from the patient for this case report.

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CASE REPORT
McGill Journal of Medicine

Distal Radial Artery Ligation for Dialysis Access Steal Syndrome

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ETHICS STATEMENT

Patient verbal and written consent was obtained for this case report. Patient demographic details have been modified where applicable to maintain patient confidentiality and only clinically relevant details are used. Ethics Committee approval was not required for this case report.

ABSTRACT

Renal replacement therapy is the definitive treatment for end-stage renal disease apart from transplant. Steal syndrome, which can lead to distal limb ischemia, is a rare but serious complication in patients who undergo hemodialysis with an arteriovenous fistula. We present a case of a 48-year-old female with limited options for dialysis access who presented with symptoms of steal syndrome. Given the need to keep her current fistula, we opted to treat her with distal radial artery ligation. This case report summarizes the various surgical techniques available for treating dialysis access-associated steal syndrome and why distal radial artery ligation should be considered a viable management strategy, especially in the context of our patient.

KEYWORDS

Renal replacement, Dialysis, Vascular surgery, Fistula, Steal syndrome, AV fistula, Ischemia

1 | INTRODUCTION

For patients with end-stage renal disease (ESRD), renal replacement therapy is the only available treatment option unless a transplant is indicated. Patients have the option of undergoing hemodialysis or peritoneal dialysis. For hemodialysis, access can be achieved through surgical creation of an arteriovenous (AV) graft, insertion of a hemodialysis catheter, or by creation of an arteriovenous fistula (AVF). Radiocephalic fistulas are the most frequently created access fistulas. (1)

On average, the maturation rate of radiocephalic fistula is about 75%. (2) For those that do mature, we then consider the development of complications with the fistula. Complications, although rare, can be serious. They include bleeding, infection, neuropathy leading to carpal tunnel syndrome, hand venous hypertension, radial artery segmental occlusion, aneurysmal dilation of

the axillary and brachial arteries, and thrombosis. (1) A steal phenomenon may also occur causing retrograde flow in the radial artery distal to the anastomosis. Physiologic steal occurs due to the flow shunt and can be seen in about 70% of all radiocephalic fistulas. (3) However, ischemic steal phenomena that contribute to distal hand ischemia and other complications are known as dialysis access-associated steal syndrome (DASS). DASS is a rare complication and occurs in 1-2% of all radiocephalic fistulae. (3)

We present a case of DASS in a 48-year-old female with a left forearm radiocephalic fistula successfully treated with distal radial artery ligation (DRAL).

2 | CASE DESCRIPTION

Patient is a 48-year-old female with a history of ESRD secondary to IgA nephropathy, failed kidney transplant, numerous failed peritoneal dialysis catheters, and is currently hemodialysis dependent via a left forearm radiocephalic fistula. She presents to a dialysis access clinic with symptoms of hand weakness along with pain, paresthesia, and discolouration. Pain was localized to the hand with no specific distribution to the fingers, which had been progressively worsening over the course of 5-6 months. Physical exam revealed an easily palpable thrill in her fistula and palpable ulnar and radial pulses. We performed a bedside ultrasound to assess the patency and flow in the arteries and veins. The patient was then assessed with a formal ultrasound and fistulogram.

A formal ultrasound was performed to assess the direction of flow in the distal radial and ulnar arteries, and in the proximal and distal radiocephalic anastomosis. There was antegrade flow in the ulnar artery which exclusively supplies the palmar arch. Proximal to the level of the radial cephalic fistula, there was normal antegrade flow in the proximal radial artery (Fig. 1A). However, distal to the level of the fistula, there was abnormal retrograde flow in the distal radial artery consistent with an arterial steal phenomenon (Fig. 1B)

A fistulogram demonstrated wide patency of the radial artery, radiocephalic anastomosis, and forearm cephalic vein. Retrograde flow in the left distal radial artery also suggests an arterial steal phenomenon. No flow-limiting stenosis was seen in the superficial or deep palmar arch (Fig. 2).

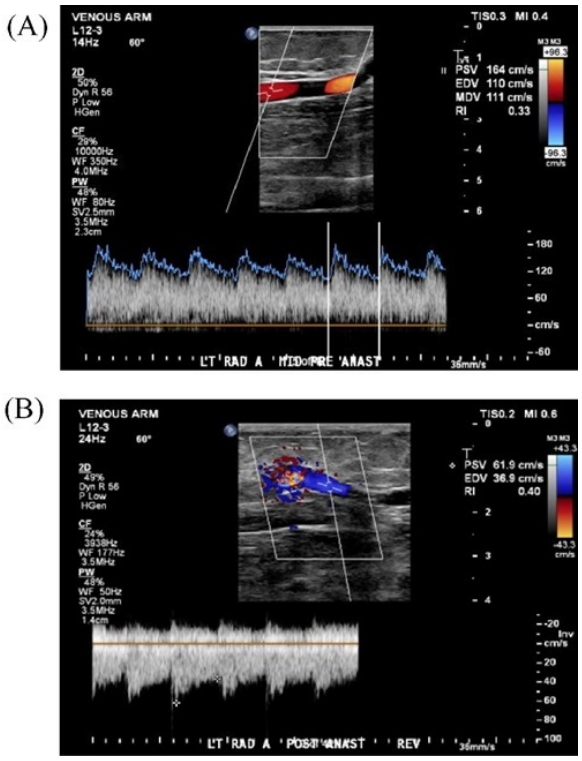

FIGURE 1 Ultrasound Doppler assessment of radial artery flows.

(A) Doppler of the radial artery proximal to the level of the anastomosis demonstrating anterograde flow.

(B) Doppler of the radial artery distal to the level of the anastomosis demonstrating retrograde flow as evidenced by reversed flow velocities. The anastomosis is demonstrated in the upper left portion of the Doppler window where there is speckling of the flow diagram.

Given that the patient had a distal radiocephalic fistula, DASS was at the top of our differential diagnosis. Other conditions that cause neuropathy were considered on our differential. Carpal tunnel syndrome was suspected; however, the patient did not notice temporal changes to her symptoms, nor did she reveal any signs on physical exam. Vasculitis that causes nerve ischemia or diabetic neuropathy were both considered as well, but the patient did not have a past medical history suggestive of these. Lastly, abscess or hematoma related

neuropathy was also part of the differential diagnosis.

3 | TREATMENT

Ultrasound was used to mark the radial artery preoperatively. We made a small 2-cm incision, dissected and identified the radial artery, and encircled it with a vessel loop. We performed Doppler analysis of the radial artery with temporary ligation of the distal radial artery and the flow became triphasic, which is normal for peripheral arteries. Satisfied with the Doppler, the distal radial artery was formally ligated. Successful ligation of the artery resulted in a good, sustained flow into the ulnar artery and palmar arches as witnessed by the Doppler. The AVF maintained a very strong thrill. We were able to successfully ligate the radial artery distal to the AVF and maintain good forward flow into the hand via the ulnar artery without compromising flow into the fistula.

4 | OUTCOME AND FOLLOW-UP

The patient was stable out of the operation and recovered without complications. Subjectively, the patient experienced symptomatic relief immediately after the recovery phase. The patient was doing well upon discharge with no compromise in AVF function. At her 9-month follow-up, she was self-cannulating her left forearm fistula successfully using two-needle rope ladder cannulation and running at our institution's maximum dialysis speed. Point-of-care ultrasound demonstrated transonic flows at 1700-1780 mL/min, suggesting normal flow.

5 | DISCUSSION

There are many strategies to approach DASS: distal radial artery embolization (DRAL), proximal radial artery ligation (PRAL) for reduction of flow, revision using distal inflow (RUDI), distal revascularization and interval ligation (DRIL), proximalization of the arterial inflow (PAI), fistula banding, and ligation of the fistula. (4) The most common intervention is ligation of the AVF and creation of a new fistula in another location.

With our patient, preservation of fistula access was important due to her history of repeated failures of intraperitoneal catheters and thrombosis of central access lines, notwithstanding the fact that central lines are not permanent solutions for dialysis access. The main deci-

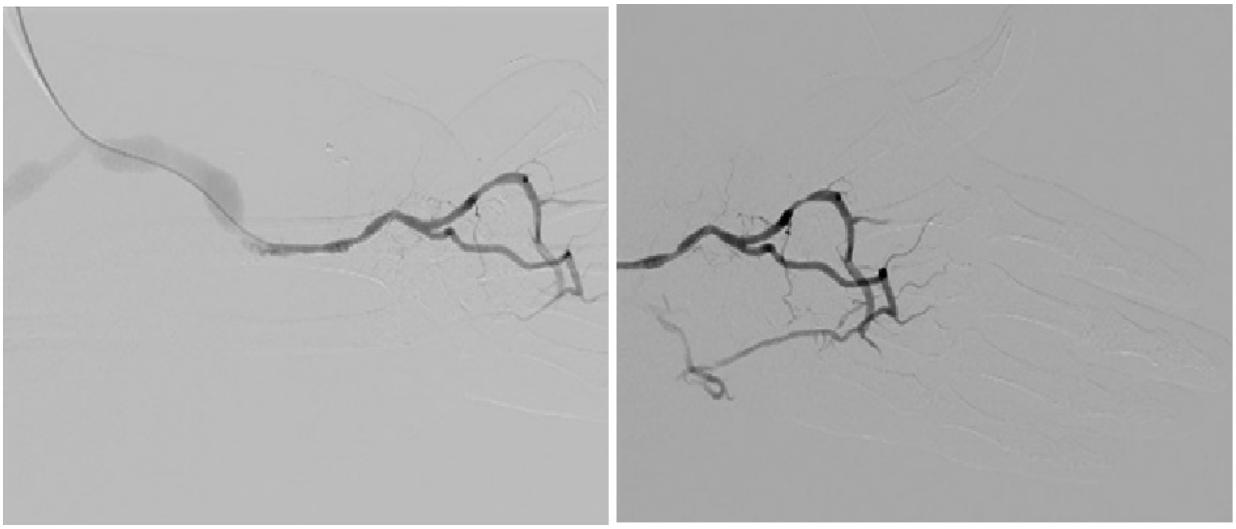

FIGURE 2 Left forearm fistulogram sequential images – catheterization of the distal radial showing patent superficial and deep palmar arch arteries. There is limited filling of the ulnar artery due to retrograde flow in the distal radial artery.

sion for this patient then was to either create a new fistula or to salvage the current fistula. Creation of a more proximal fistula in this patient was not ideal since DASS is more common for proximal fistulas. (3) Ligation of the current fistula and creating a new fistula in the other arm was not a preferred option as she is a young patient and we wanted to preserve future access sites. Therefore, effort was made to salvage her current fistula.

We can then approach the various treatment procedures in terms of the end goal of reducing flow across the fistula. With regards to actual intervention at the level of the fistula, banding decreases the diameter of the fistula, thus increasing resistance and decreasing flow. We can also think of altering the sources of flow that contribute to the steal phenomenon. These include PRAL, RUDI, DRIL and DRAL. PRAL, RUDI and DRIL are employed for more proximal AVFs such as brachiocephalic fistulas, which our patient did not have. Options for our case thus included fistula banding, PRAL, and DRAL. For our patient, fistula banding was not pursued since it has a higher re-intervention rate and a higher rate of access thrombosis. (4) PRAL was not selected since the surgeon was concerned that it may compromise flow to the fistula thus rendering it non-functional. It is estimated that one-third of radiocephalic fistula flow is supplied by the distal radial artery, so by preserving proximal flow, which conversely supplies two thirds of normal fistula flow, we may theoretically conserve flow through the fistula. (5) Although distal radial artery embolization is a newer technique, DRAL should still be considered given its ease and ability to assess flow intraoperatively. For the above reasons and surgeon experience, DRAL was chosen as the ideal approach for this patient.

Ultrasound is vital in our approach to our patient. Preoperative examination using colour doppler ultrasound can be used to predict the success of DRAL. (6) It is therefore beneficial to use point-of-care ultrasound in the initial assessment in the clinic to help guide therapy.

DRAL is an effective procedure and should be considered. A study of patients with DASS within a 5-year period from one centre demonstrated that procedures were mostly ligation (50%) or banding (38%). (4) However, our case demonstrates that DRAL is a viable and effective treatment for radiocephalic fistulas. Disruption of distal flow using DRAL has been shown to be very efficacious with small subpopulations in epidemiologic studies showing 100% symptom resolution with no vascular comorbidities. (4,7) In a study looking at 15 DASS patients where 5 of which underwent DRAL, all showed significant clinical improvement in clinical symptoms. Of the patients with DRAL, 3 of the 5 had complete resolution. The two patients with partial resolution had complications due to significant pre-existing comorbidities. Hence, DRAL is an efficacious technique in most DASS patients with radiocephalic fistulas.

6 | LEARNING POINTS AND CONCLUSION

Patient context will often guide one's therapeutic decision making. In our case, our dialysis patient was experiencing DASS with a history of multiple failed access attempts using intraperitoneal dialysis. The patient's young age also pushed us toward trying to salvage the current fistula as opposed to ligating the current fistula and creating a more proximal fistula. Given her age and dependency on fistula access, it was more advisable to maintain access options for the future.

Ultrasound and angiographic assessment are vital in determining the success of a DRAL procedure and should be a part of any work-up in deciding treatment for DASS. With our patient, DRAL is a successful treatment for DASS. Disruption of distal radial artery flow has been shown to be a successful strategy in relieving ischemic steal-related symptoms. (7) Given appropriate collateral flow from the ulnar into the palmar arch, DRAL should be considered in patients with radiocephalic fistula DASS.

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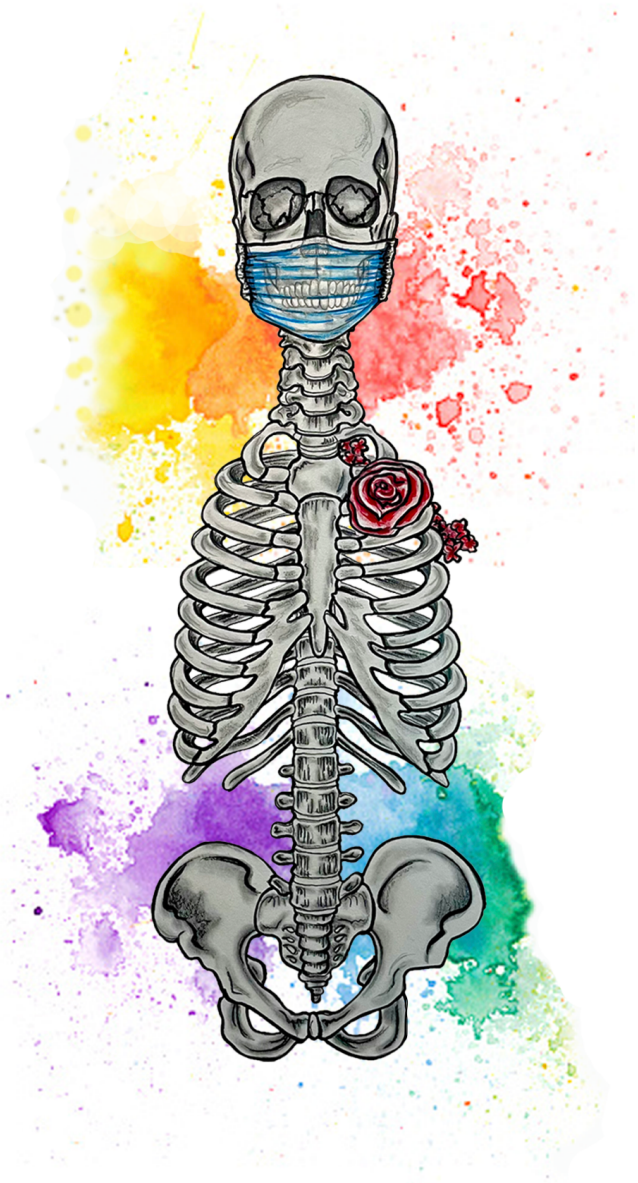
COMMENTARY



Artist: Caroline Najjar

COMMENTARY
McGill Journal of Medicine

Social Media and Mental Health: What We Know

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ABSTRACT

There are seemingly opposing findings on social media's effect on mental well-being. While some studies report detrimental effects, others report no association, and others still report positive or buffering effects. However, social media has rapidly evolved over a short span of time, and so has people's use of social media platforms. Collecting an accurate measure of social media use and other methodological challenges particularly affect the data in this area. In this commentary, we discuss two longitudinal studies to reconcile the contradictory findings on the effect of social media use on mental health.

KEYWORDS
Social media, Mental health, Commentary, Opposing findings

1 | INTRODUCTION

During the COVID-19 pandemic, the issue of social media use and mental health has become particularly salient, with the pandemic bringing an increase in socialization through online platforms to respect social distancing rules. Systematic review evidence has quickly tried to answer growing concerns about the effect of increased social media use on mental health; for instance, one review identified social media exposure as a risk factor for the newly observed high rates of anxiety, depression, and other psychological distress in the general population of several countries. (1) In the pre-COVID-19 literature, meta-analyses caution against "dramatic claims" of the "mischief " of social media. (2) For instance, Appel et al. (2020) noted small associations between intensity of social networking use and school achievement, depression, life satisfaction, and more. Frost and Rickwood (2017) also reported a mix of evidence and restated the need for comparing single or similar platforms. (3) A review of the Bergen Addiction Scales for social media use found small negative associations between addictive social media use and well-being. (4) Some studies are even optimistic, with a 2019 review finding that Facebook-based social support had positive effects on well-being. (5) For some populations, there may be especial con-

cern. Several studies more cautiously interpreted the evidence, identifying links with risky behaviour in adolescents, (6) harmful social comparisons, (7) and maladaptive personality traits. (8)

Many research studies have found opposing results of social media's impact on mental health. Even systematic reviews, which consider the heterogeneity of studies and various methodological challenges, come to different conclusions. Thus, a detailed case-by-case analysis may be advantageous. In this commentary, we describe the methodologies of two studies which we chose given their longitudinal design, recency, and impact (with nearly 350 citations between the two). (9, 10) In effect, we provide a summary of if and how social media use can have opposing effects on well-being using two studies. We highlight the particularities of studies in this area that are among the potential reasons for these differing findings, provide examples of their effects, and make recommendations for future work.

2 | SOCIAL MEDIA USE AND MENTAL HEALTH AMONG ADULTS

2.1 | Study Objectives and Background

The *American Journal of Epidemiology* published an article in 2017 tracking the longitudinal associations between Facebook use and well-being. (10) Given the "ubiquity of online social networking sites" and the considerable impact of social relationships on well-being, including lowering mental health risks, negative health behaviours, mortality, and morbidity, the authors identified a need for longitudinal, objective data on the potential risks and benefits of social media use on well-being. Thus, Shakya and Christakis (2017) compared the longitudinal associations of real-world social networks and Facebook use with four aspects of well-being: self-reported mental health, life satisfaction, physical health, and body mass index (BMI). Additionally, they controlled for the buffering effect of in-person social networks on social media use.

2.2 | Methods

The data collection occurred in three waves over a three-year period, recruiting from a nationally representative online panel of American households (Gallup Panel 2013-2015). Approximately 40,000 Gallup Panel members were randomly selected and emailed an invitation across the three waves of the study (n=10,680 respondents across three waves). Among the measures were self-reported well-being and life satisfaction, as well as objective measures of social networking use. When granted access, the researchers recorded the participants' number of friends on Facebook (*friend count*), likes since the creation of the account (*lifetime like count*), links clicked in the last 30 days (*link count*), and status updates in the last 30 days (*status count*). Participants provided height and weight data for calculation of BMI. The participants also provided their number of friends, closeness with them, and the number of face-to-face interactions with friends per week in a friend nomination exercise.

The statistical analyses included linear regression and prospective multivariate analyses. Interestingly, the authors chose to conduct both cross-sectional and prospective analyses with stacked data (compiling Waves 1, 2, or 3 into one dataset in various combinations). Less than 5% of all participants responded to each of the three waves, but the authors adjusted the stacked data for potential clustering as a precautionary measure. They also controlled for wave-level fixed effects and several demographic variables (income, educational level, age, sex, marital status, race, and Hispanic ethnicity). Each of their self-reported measures were standardized into *z-scores*.

2.3 | Results

Participants who shared their social media data with study authors were significantly different from those who did not, being younger in age, having attained a higher level of education, more likely to be female, and unmarried. Those who shared data also reported lower baseline scores of mental health and life satisfaction, a

higher number of friends, and less time spent interacting with friends ($p<0.001$ for each variable).

The study found that Facebook use is associated with worse mental health. Though a greater number of Facebook friends was significantly associated with better mental health, a greater lifetime like count, 30-day link click count, and status update count were all significantly associated with worse mental health. All associations with mental well-being were significant in cross-sectional and prospective analyses, except for nominating more friends and spending more time with friends, which lost significance prospectively. Similar negative associations were found for life satisfaction and Facebook use. Following prospective analyses, most of the described associations remained significant, except status count and interaction with friends. Lastly, social media use was associated with worse self-reported physical health and higher BMI.

Conversely, reporting greater closeness with friends and interacting with them more frequently in-person were associated with improved mental health. Considering the possibility that individuals experiencing social isolation may be more likely to use Facebook, the authors adjusted for the number of friends and average closeness with friends in their models, and all results remained significant.

3 | SOCIAL MEDIA USE AND MENTAL HEALTH IN ADOLESCENCE AND EMERGING ADULTHOOD

3.1 | Study Objectives and Background

Previously reported cross-sectional and longitudinal studies have relied on traditional regression techniques that solely model between-person relations among variables and have ignored the examination of opposing directions of effects between mental health and social media use. Moreover, many studies have short follow-up periods (i.e., months to 2 years), which limits the investigation of social media use across development. To respond to the limitations in the literature, Coyne et al. (2020) published a longitudinal study examining a causal model of the associations between time spent using social media and mental health (depression and anxiety) during the transition from adolescence to emerging adulthood in *Computers in Human Behavior*.

3.2 | Methods

This eight-year (2009-2016) study recruited participants from another study on inner family life. Participants between the ages of 10 and 13 were recruited from a large Northwestern city in the United States via database, referrals, and flyers. Interviewers conducted assessments in participants' homes, and the analyses from the present study were taken from the data collected via questionnaires.

Social media use was measured with the question, "How much time do you spend on social networking sites, like Facebook, on a typical day?" Depression was measured using the Centre for Epidemiological Studies Depression Scale for Children (CES-DC). (11) Anxiety was measured using the Spence Child Anxiety Inventory. (12) To disentangle the within- and between-person sources of variance in this longitudinal study, the authors used an autoregressive latent trajectory model with structured residuals. Trait-like and stable individual characteristics (e.g. ethnicity) were controlled for by the model design. To conduct analyses, the authors restructured participants' age during the study so that the variables could be considered when the participants were the same age, and they accounted for missing data with imputation.

3.3 | Results

Coyne et al. found that social media use increases throughout adolescence. At 13 years old, adolescents spent 31-60 minutes per day using social media, with levels increasing steadily up to two hours per day for young adults. Age and gender moderated the association of social media use with depression and anxiety. Social networking at age 13 was positively correlated with depressive symptoms for girls, but rates of change were not associated. For boys, social networking and depres-

sive symptoms were initially unrelated at age 13, but rates of change in social networking covaried with an increase in depressive symptoms. Yet, those with more social networking at age 13 showed higher levels of anxiety at that age, and more rapid increases in social networking were associated with more rapid increases in anxiety symptoms.

The results also indicated no future prediction of anxiety and depression. Increases in adolescents' social networking beyond their typical levels could not explain changes in depressive symptoms one year later. Similarly, depressive symptoms at a given age were mostly unrelated to social networking in the following year, except at age 16, in which depressive symptoms predicted lower use of social networking at age 17. Social networking did not predict future anxiety, and anxiety did not predict future social networking. While adolescents with higher social media use have more mental health challenges on average, their individualized fluctuations in social media use were not associated with changes in their mental health.

4 | COMPARABILITY OF MENTAL HEALTH AND SOCIAL MEDIA STUDIES

Shakya and Christakis reported that the use of Facebook was generally negatively associated with well-being. Conversely, Coyne et al. did not find associations between time spent using social media and mental health outcomes from early adolescence into young adulthood. These conflicting findings may be due to differences between objectives and methodologies, which weaken the supposition of contradicting literature. A summary of the articles' methods and results are provided in Table 1.

4.1 | Objectives and Research Question Differences

One explanation for seemingly opposing findings may be different objectives and even research questions. Coyne et al. examined associations between time spent using social media and mental health (depression and anxiety) during the transition from adolescence to emerging adulthood. On the other hand, Shakya and Christakis examined the associations of real-world social networks and Facebook use with well-being measured as a broader construct (mental health, life satisfaction, physical health, and BMI). In congruence with the distinct objectives of the studies, the methodology differed.

4.2 | Methods

4.2.1 | Sample Characteristics: Data availability and Historical Factors are Important Limitations

Shakya and Christakis examined social media use in a limited sample of adults within the general population. While they used a subset of participants from a nationally representative sample, the final sample was considerably smaller once they excluded participants who had not provided data for the three assessment waves, and even more so when including only participants who agreed to use of their Facebook data. The exclusion of individuals who were not comfortable sharing this private data limits the generalizability of their findings to the general population and to Coyne et al. Further supporting this argument, the authors reported that participants who shared their data were significantly different from those who did not on several variables that are known to impact mental health, such as a greater number of women, less likely to be married, lower scores on mental health and life satisfaction, and less spent time spent interacting with friends.

In Coyne et al., the sample was composed of adolescents, particularly from what the authors defined as Generation Z ("iGen"). iGen represents those born into a world with ubiquitous smartphone use, technological advancement, Internet accessibility, and social media use. Consequently, individuals of this generation are found to spend more time using devices than previous generations. (13-15) The authors in this study defined

Publication	Shakya and Christakis (2017)	Coyne et al. (2020)
Methods		
Follow-up	Three-year longitudinal study (2013-2015)	Eight-year longitudinal study (2009-2016)
Sample	• Adults within the general population (data from nationally representative online panel of American households) • N = 71,833 participants across 3 waves; 6,730 included in analysis (those who provided access to Facebook data) • Average age of 48.4 years • 58% female	• Children between the ages of 10 and 13 recruited from a large northwestern city in the United States (via a database, referrals, and flyers) • N = 487 participants retained over the eight years of the study (83% retention rate) • Average age of 13.8 years • 51.6% female
Data	• Data on both in-person and online social networks (Facebook only)	• Data from online social networks (e.g., Facebook and Instagram)
Measures	Mental Health • One item on a rating scale of 1 indicating *poor*, 2 indicating *fair*, 3 indicating *good*, and 4 indicating *excellent* Objective measures of Facebook use • Friend count • Lifetime like count • Link click count • Status count	Mental Health • Depression: The Centre for Epidemiological Studies Depression Scale for Children (CES-DC) • Anxiety: The Spence Child Anxiety Inventory Social media use • "How much time do you spend on social networking sites, like Facebook, on a typical day?"
Statistical analyses	• Linear regression • Prospective multivariate analyses with stacked data	• Autoregressive latent trajectory model with structured residuals
Covariates	• Income, education level, race, age, sex, marital status, Hispanic ethnicity	• Trait-like and stable characteristics (e.g., ethnicity) controlled by within- and between-person variance
Results		
Association between social media use and mental health	• Greater number of Facebook friends was significantly associated with better mental health. • Greater lifetime like count, 30-day link click count, and status update count were significantly associated with worse mental health. • Almost all associations remained consistent in directionality and significance across prospective analyses.	• For girls aged 13, social networking positively correlated with depressive symptoms but not rates of change. • For boys aged 13, social networking and depressive symptoms were not associated, but rates of change in social networking covaried with change in depressive symptoms. • Higher social networking at age 13 correlated with higher levels of anxiety at age 13. • More rapid increases in social networking correlated with more rapid increases in anxiety symptoms.

TABLE 1 Comparison of studies examined

iGen as those born between 1993 and 1997. However, this is inconsistent with the Pew Research Center definition of Generation Z, which is those born between 1997 and 2012. The preceding generation, known as Millennials, are those born between 1981 and 1996. (16) Other studies examining the iGen generation are generally consistent with these definitions. (13, 15, 17)

While Coyne et al. described little effect of social media among iGen, their sampling is somewhat inconsistent. Firstly, 15% of the sample was recruited in a manner different from the rest, yet no group-level differences were analyzed. Coyne et al.'s sample is also not consistent with the ranges described, being a study of individuals born in the years 1993-1997 and not actually a part of the iGen generation. Their sample, instead, is representative of a relatively small bracket of Millennials who grew up as widespread smartphone use first began and social media was developing.

When studying social media's effects on mental health, historical factors like generation and the evolution of technology at the time are both important caveats. Data collection for Coyne et al. began in 2009, a time when social media networks had recently launched and were rapidly changing. For context, Facebook was launched to the public in 2006, Instagram launched in 2010, and Snapchat first launched in 2011. While Coyne et al.'s findings on social media and mental health may have been true at the time, it is questionable whether they still apply. Thus, the paper must carefully be considered within its context. More current studies report that adolescents aged 12 to 18 use up to 7 hours and 22 minutes of social media per day, (18) whereas Coyne et al. found an average of 30 minutes of daily use among the first wave of 13-year-old participants. The article's application to the current context is thus considered a weak point.

A strength of Coyne et al. over Shakya and Christakis was their coverage of a broader developmental period, disaggregating the effects of age on associations between social media use and well-being. While both studies were longitudinal in design, they varied in the length of the follow-up period. Coyne et al. were able to study this issue over an 8-year period, which is much longer than most similar studies. The length of the follow-up period allowed for the study of the entire developmental period (i.e., from early adolescence into young adulthood). Contrarily, the article by Shakya and Christakis only had a 3-year follow-up, which does not allow for the investigation of different stages in development. However, this was not the purpose of this study, and a longer follow-up period may not be necessary when studying older age groups.

4.2.2 | Self-Reported Social Media Use is Different from Objective Markers

There are differing measures for social media use and mental well-being, each with their own strengths and weaknesses. Typically, there is concern about one-item self-reported measures, and especially those that have not been psychometrically validated, as used in Shakya and Christakis. It is questionable whether one item can fully represent complex concepts like mental health and life satisfaction. Coyne et al. also used self-reported measures; however, they used well-known and validated scales for depression and anxiety. Yet, these measures are equally criticized for their specificity to symptoms of mental disorders, potentially missing broader dimensions of well-being such as those in Shakya and Christakis. A final consideration is the use of objective measures of social media use, like Shakya and Christakis's multiple indices of Facebook, while some others like Coyne et al. may use single-item or self-reported measures of social media use, despite other studies suggesting that people under-report their social media use.

4.2.3 | Statistical Analyses: The Importance of Within-Person Variance, Effect Sizes, and Controlling for Covariates

The regression techniques used by Shakya and Christakis only model between-person relations among variables, thus ignoring the individual processes that are important to understanding the true relationship between these variables. In contrast, Coyne et al. used rigorous statistical techniques to examine the within-person as-

sociations between social media use and mental health. Thus, disaggregating the between- and within-person effects can provide a more comprehensive understanding of the relationship between mental health and social media use. Shakya and Christakis only tested for unidirectional effects (i.e. the effect of social media use on mental health), but Coyne et al. found that mental health can influence people's time spent on social media. Indeed, Coyne et al. used two well-known theories within the field to guide their research design, which prompted them to also examine whether mental health influenced duration of social media use.

Although some findings may demonstrate statistical significance, the implications in the real world are still unknown. For instance, Shakya and Christakis reported small effect sizes for their findings. A recent study using three nationally representative datasets from the U.S. and the U.K. found that digital technology use was associated with well-being to the same extent as eating potatoes regularly. (19) Another recent large-scale national study in New Zealand reported that the association between time spent on social media and psychological distress was very weak, with only excessive amounts resulting in changes in level of distress. (20) Additionally, covariates may partially explain some findings. Although Shakya and Christakis controlled for sociodemographic variables, several important confounding variables were not considered, including physical health and substance use (e.g. smoking, alcohol use, medication, etc.). For example, significant distress has been reported in individuals suffering from physical health conditions, and smoking is associated with poorer mental health outcomes (i.e., symptoms of depression and anxiety). (21-24)

5 | CONCLUSIONS

In our critical analysis of some of the key issues involved in research on social media and mental health, we chose two influential and recent longitudinal studies, both of which had several strengths to their designs and had an impact on the literature on social media. Nevertheless, each had some critical limitations and weaknesses, which made their comparison difficult and highlights some important standards for future studies on social media to achieve peak generalizability and validity. First, data collection and availability are a key issue. There are clear benefits to more objective and multi-item measures of social media use as seen in Shakya et al., such as avoidance of the social desirability effect and recall bias. This approach also allows a more accurate examination of the impact of the different aspects of social media on mental health, avoiding broad generalizations about these complex technologies. Nevertheless, Shakya et al. also exemplifies more methodologically taxing issues of data availability and sampling bias, which are risks that accompany use of more objective and invasive measures. Second, as technology continues to evolve at accelerating rates, researchers must be careful of generational effects, especially when attempting to generalize their findings. Third, future research should carefully examine the moderators of social media's effects on mental health, such as stages of development and person-to-person variance, when assessing the risks of social media.

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COMMENTARY
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Effectiveness of Home-Based Cardiac Rehabilitation and Its Importance During COVID-19

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ABSTRACT

Cardiac rehabilitation is a secondary prevention and disease-management opportunity for individuals living with cardiovascular disease. The COVID-19 pandemic has caused postponements and cancellations for many health services, including 41% of cardiac rehabilitation programs in Canada. Cardiac rehabilitation effectively reduces the risk of mortality, morbidity, and hospitalizations in cardiac clients. Without access, individuals face challenges to improve their health, which places them at risk of adverse outcomes. This paper argues that transitioning to home-based cardiac rehabilitation programs during the pandemic is a reasonable strategy to meet the ongoing rehabilitation needs of cardiac patients. Home-based cardiac rehabilitation programs utilize limited hospital or clinic visits because the majority of exercise is performed at home through regular communication with a case manager. Programs utilize a variety of resources, including technology, to regularly monitor, educate, and counsel clients. The programs' flexibility and convenience overcome many multi-level barriers which normally impede participants from accessing services. These programs have proven to be equally effective, if not more effective than centre-based programs, at improving mortality, cardiac events, exercise capacity and modifiable risk factors. Home-based programs are a valid alternative to support and protect a vulnerable population, especially those at high risk if diagnosed with COVID-19. Transitioning to a home-based platform may be a challenge, but the Canadian Cardiovascular Society has provided practical approaches to support programs. Adapting current plans and developing new ones, utilizing appropriate resources, having a conservative exercise program, monitoring clients, emphasizing education, being flexible, and enhancing safety are key steps for a successful transition.

KEYWORDS
Cardiac Rehabilitation, COVID-19, Home-Based, Tele-Rehabilitation, Virtual Health

1 | INTRODUCTION

The novel coronavirus disease (COVID-19) was declared a global pandemic in March 2020 and has caused disturbances in every aspect of life, particularly for vulnerable groups such as those living with chronic disease. (1,2,3) The pandemic has caused many disturbances in healthcare by cancelling or postponing services to prevent the spread of COVID-19 and prepare for a potential surge in patients that could deplete resources. (4) This included the closure of approximately 41% of cardiac rehabilitation (CR) programs across Canada. (5) These closures can potentially cause adverse short- and long-term consequences for attendees, such as increased rates of cardiac events, emergency room visits, hospital admissions, and potential exposure to COVID-19, consequently further depleting healthcare resources. (6,7) CR is defined as "the enhancement and maintenance of cardiovascular health through individualized programs designed to optimize physical, psychological, social, vocational, and emotional status." (8) CR is a secondary prevention and disease-management opportunity for those who have experienced an acute cardiac event, those with chronic cardiovascular disease, those who have undergone cardiovascular procedures, and those with cardiovascular risk factors. (9, 10) Through health education and self-management opportunities, CR aims to reverse or prevent disease progression and reduce the recurrence of cardiac events, helping participants improve and take control of their health and wellbeing. (8)

COVID-19 has made it more challenging for this group to engage with resources such as CR due to closures. Alternative ways to deliver care are recommended and have been implemented for many healthcare services, and CR should be no different. (4) In Ontario, only about 10% of CR participants undergo home-based CR, often due to clinical factors such as those at high risk of complications or those with a low functional status requiring more supervision. (11) Home-based CR is a highly underutilized resource shown to be just as effective as centre-based programs when implemented appropriately. (12-19) Through advocacy and innovation, healthcare providers and health leaders can utilize new and existing strategies to meet the current challenge of delivering this important component of rehabilitation. Doing so will enable people to achieve optimal health gains by properly managing their cardiovascular disease. The following paper suggests that given the current COVID-19-related constraints on in-person health services, transitioning to a home-based CR program is a reasonable strategy that will enable clinicians and administrators to meet the ongoing rehabilitation needs of cardiac clients.

2 | CARDIAC REHABILITATION IN CANADA PRE-PANDEMIC

Cardiovascular disease is the second leading cause of death in Canada and the leading cause of death globally, with 8.9 million deaths worldwide in 2015. (20) Between 2012 and 2013, about 2.4 million Canadians were living with cardiovascular disease. (20) All-cause mortality rates for cardiovascular disease have declined over the years, reflecting improvements in treatment, disease management, rehabilitation, and public health interventions. (20) As more people survive acute cardiac events and continue to live with cardiovascular disease, they may also experience negative impacts on their quality of life for a longer period of time. (20) Programs such as CR are essential to optimize recovery and limit mortality.

CR programs have been proven to reduce the risk of cardiovascular mortality, morbidity, and hospitalization through the use of a therapeutic process involving five core components: (i) risk factor assessment and management, (ii) structured exercise training, (iii) nutrition counselling, (iv) patient education, and (v) psychosocial counselling. (8, 21-25) In Ontario, a retrospective matched cohort study found that CR reduces mortality by 50% when comparing CR versus non CR participants in a sample of matched hospitalized cardiac clients. (25) Over 200 CR programs in Canada are delivered primarily in a supervised center-based facility by an interprofessional team of healthcare providers. (11, 26) Typically, programs offer two multi-dimensional sessions per

week that consist of exercise, education, assessment, and counselling that are delivered over a period of five months. (11)

Although the benefits of CR have been shown, this resource is still widely unavailable and underused, with only 75-80% of eligible individuals participating, due to multi-level barriers such as low referral rates, geographic location, financial constraints, inequitable access, and more. (7, 11, 24, 27-31) In Canada, there is only one CR spot per 4.55 people who require it, and 186,187 more spots are needed annually to meet current demands. (32) Ontario would need about 35,183 more CR spots to treat those identified through hospitalization alone. (11) The literature shows that CR availability and accessibility is an issue, and the new COVID-19 pandemic has added considerable complications for those delivering programs and individuals requiring the service.

3 | IMPACT OF COVID-19 ON CARDIAC REHABILITATION PROGRAMS

Approximately 41% of CR programs in Canada completely closed at some point during the COVID-19 pandemic. (5) In-person services were cancelled or postponed due to recommendations by governments and public health agencies to limit the spread of the virus. (6, 7, 33) Closures were mainly a result of staff redeployment, facilities being located in a hospital or high-risk facility, repurposing the facility for use in the effort against COVID-19, lack of funding, and lack of leadership. (5) CR programs that had established virtual home-based programs pre-pandemic as an alternative or supplement to their centre-based program were able to implement that full time. (5, 7) In contrast, others had to create and transition from their regular programs to an entirely home-based program. (5) As such, fewer services were offered, with many being delivered through the telephone, email, postal mail, or web-based platforms, posing new challenges for clients and healthcare providers. (5, 7)

With lockdowns and physical distancing measures in place, individuals living with cardiovascular disease are at a greater risk of increasing their sedentary choices, decreasing physical activity, making poor nutrition choices, and suffering from mental health issues, thus increasing their risk of acute cardiovascular events and long-term consequences. (7, 33) In the absence of CR programs, individuals are unable to engage in valuable health education on cardiovascular risk, health nutrition, cognitive and behavioural symptom management, and safe exercise habits with the guidance and support of a healthcare provider.

In addition, the impact of COVID-19 is more severe in older adults living with comorbidities. (2, 3) Case-fatality rate is 8.0% in those aged 70 to 79, 14.8% in those aged 80 and older, and 10.5% specifically in those with cardiovascular disease. (2) With the majority of individuals living with cardiovascular disease being 65 years and older, they are at high risk if diagnosed with COVID-19. Maintaining resources, such as CR, that promote and protect their health is critical during this time. (2, 34)

Although programs have rightly sought to limit the spread of COVID-19 and protect a vulnerable population, the short- and long-term consequences of these actions may result in collateral declines in health that could have serious implications for the individuals and the health system. Alternatives such as home-based programs can be instated to offset these potential consequences.

4 | HOME-BASED CARDIAC REHABILITATION PROGRAMS

4.1 | Structure

The Canadian Cardiac Rehabilitation Association explains that home-based CR programs utilize limited hospital or clinic visits, typically for low to moderate risk cardiac clients. (8) The majority of exercise training is performed at home through regular communication with a case manager for follow-up, education, and counselling. (8, 24, 35-37) Some programs may use advanced tech-

nology with clients wearing sensors for real-time monitoring of physiological signs by healthcare providers. (38) Regardless of the program structure, frequent and regular monitoring is always integral to all programs whether this monitoring be through in-person meetings, mail, telephone, email, or online chat sessions. (17, 24, 30, 33, 39) Independence is a key component, relying on the client's ability and motivation to self-manage. These programs have been introduced as a potential strategy to overcome some of the multi-level barriers experienced by individuals and programs when trying to offer and engage in traditional centre-based CR.

4.2 | Answer to Multi-Level Barriers

Multi-level barriers to CR occur at the individual, program, community, and health system levels. Individuals face issues like geographic location, transportation, financial factors (costs associated with attending in person such as parking and transit), and inclement weather. (11, 24, 27-31) Individuals may also suffer from comorbidities or compromised functional abilities, making it challenging to attend appointments in-person. (24, 29, 30) Furthermore, home and professional responsibilities may further constrain clients' ability to attend appointments. (24, 27, 30) Additionally, individuals from marginalized groups such as those with low socioeconomic status, minority, and vulnerable groups have a disproportionately more difficult time accessing CR. (11, 27, 30)

At the program level, facilities can be constrained by space, personnel, or financial limitations, and they may be unable to offer the appropriate calibre of program required to meet the needs of the community. (11, 30) At the community level, a common barrier includes primary care providers who are unaware of available CR programs and its associated benefits. (11, 29) This results in a lack of referrals, a primary reason why those who qualify for CR do not attend. For example, policy guidelines from the Canadian Association of Cardiac Rehabilitation and the Canadian Cardiovascular Society recommend that at least 85% of individuals who require CR should be referred for CR and at least 70% should be enrolled. However, only 52% of clients in Ontario are referred for CR. (11, 40) At the health system level, a lack of reimbursement by the government limits programs' ability to properly serve their community. (11) The inability to adequately fund CR programs across the country impacts the accessibility and uptake of CR programs. (11)

4.3 | Effectiveness of Home-Based Cardiac Rehabilitation

Research suggests that home-based CR programs are equally effective, if not more effective than centre-based CR programs at improving the health and risk factors associated with cardiovascular disease. (12, 14-19, 41) In particular, home-based CR programs have been shown to produce the same or improved rates of mortality and enhance the short and long-term exercise capacity of those who participate. (12, 13, 16, 18, 19, 28) These programs provide all of the core components of CR while being highly flexible and widely accessible. This accessibility helps overcome many of the barrier's individuals face when accessing centre-based CR programs. (12, 16, 17, 42)

A Cochrane Database Systematic Review conducted by Anderson et al. (16) identified no difference between home-based and centre-based groups regarding mortality, cardiac events, exercise capacity, modifiable risk factors such as cholesterol, blood pressure, smoking, and health-related quality of life. However, it showed higher program completion levels and adherence for those in a home-based program. (16) Another recent systematic review by Jin et al. (19) looked specifically at the impact of telehealth interventions in home-based CR programs as an alternative or adjunct to usual care (any routine care for cardiovascular disease) or centre-based CR. The authors discovered no significant difference in mortality between telehealth interventions and usual care or centre-based CR. (19) However, the interventions did show significant beneficial results in the medium and long-term duration for the secondary prevention of cardiovascular disease compared to usual care and equivalent results compared to centre-based CR. (19) When

used in combination with usual care or centre-based CR, even better results were evident. (19)

Adherence is one of the most critical aspects that determines an individuals' success in the program. Home-based CR participants often have superior adherence and completion rates than individuals receiving usual care or center-based care. (12, 14, 28, 41) This high level of adherence is due to its ability to address many barriers and its flexibility. (42, 43) Individuals have also expressed overall satisfaction with these programs. (31, 36-39, 41-43) These types of programs foster confidence, independence, and behaviour change and develop self-management skills that carry on post-program. These skills enable individuals to better their health long-term. (30, 36-38, 41-43)

Overall, research has demonstrated that home-based CR programs are effective for risk reduction and positive behavioural outcomes in clients. Such programs are a useful adjunct or alternative to centre-based CR if appropriately used.

4.4 | Challenges of Home-Based Cardiac Rehabilitation

No healthcare intervention is perfect and home-based CR is no exception. Associated challenges include technology issues, lack of peer support, lack of motivation, lack of supervision, and privacy issues. (7, 33, 37-39, 42, 43) A variety of technology issues can determine a participant's access and ability to successfully engage in home-based CR programs. For example, limitations pertaining to digital access can make it challenging to access virtual resources, inhibiting participant's ability to learn. (7, 37, 38, 42, 43) In addition, a lack of digital literacy can hinder participants' ability to fully utilize virtual resources. (37, 39, 42, 43) Appropriate training is required for health providers and clients engaging with virtual platforms. (5) Furthermore, use of digital technology raises concerns around privacy and security. (33, 43) Client confidentiality is necessary in all situations and the use of technology adds a layer of complexity and risk that may deter participants from engaging in such programs.

In a centre-based program, participants are surrounded by peers and healthcare providers who make the program engaging and enjoyable which in turn promotes motivation. At home however, building the motivation to promote positive results can be difficult. (39) The lack of interpersonal support can significantly impede a participant's ability to maintain motivation. As well, concerns exist of increased risk for harm without professional oversight to ensure exercises are being performed properly. (39)

5 | HOME-BASED CARDIAC REHABILITATION IN A COVID-19 WORLD

With many other health services finding alternative ways to provide care, home-based CR is a valid option to support clients. Transitioning to home-based programs will be challenging for provider organizations due to larger service requirements and increased need for resources, particularly related to digital platforms. (6)

The lack of standardized guidelines for delivery of home-based CR prior to the pandemic further complicates the process of shifting to a solely home-based format. The Canadian Cardiovascular Society (CCS) has provided some guidance on implementing virtual at home CR and included some practical approaches to support programs in their transition. (6) The overall goal is to prioritize basic, safe, and timely care until a program is established; afterwards, care should be shifted towards ensuring traditional standards are met. (6) Having an evaluation plan and adapting current plans as needed enhances sustainability. This is crucial in addressing program administration issues during the pandemic as well as gaps present prior to the pandemic. (7)

5.1 | Practical Approaches to Implementation

The CCS recommends that programs support staff in their transition towards virtual care. (6) Programs should utilize one suitable online resource for clients and staff

to access information in order to avoid being overwhelmed by the number of resources available. (6) Upon initial interaction with clients, it is important to have intake assessments that discusses the potential risks and benefits with the understanding that minimal CR support is better than none. (6, 7)

Though home-based CR programs are not suitable for everyone, programs should consider all clients eligible for home-based CR in some capacity, including exercise training. (6) Though risk-stratification can be a challenge, the emphasis should be on clinical assessment and alternative ways to assess risks, such as the self-administered 6-Minute Walk Test and use of personal blood pressure machines. (6)

The CCS recommends that programs focus on CR core components, including lifestyle risk management, psychosocial supports, medical advice, education, and simple exercise prescriptions. (6) Home-based exercise programs should be conservative and slowly titrated to ensure safety. (6) Exercise programs should aim to provide the minimal level of physical activity to achieve health benefits without exceeding a moderate level of exercise intensity. (6) The use of self-assessment tools such as heart rate palpation, wearable heart rate monitors, and the 'talk test' can help determine the level of exercise intensity. (6) An increased emphasis should be placed on the signs and symptoms to monitor while exercising and the use of different technologies where available. (6)

The CCS also suggests that programs use digital platforms that enhance and facilitate program delivery, including group tele-/videoconferencing sessions, in order for education and support to reach more individuals. (6) Technology should be made available to clients in order to maximize uptake of remotely offered CR. (6) However, programs should initially plan to use and repurpose the resources they have over complex restructuring; this may include mailing paper-based education materials as required. (6, 7) Focusing on the resources available will allow for more rapid implementation of home-based programs and limit the loss of service provision to clients.

A recent study looking at the impact of COVID-19 on CR programs in Canada found that 35 of the 52 programs still running reported at least one web-based resource. (5) Technology use increased for education and the delivery of exercise programs. (5) These notions show that many programs have risen to the challenge of promoting continuity of care during the pandemic.

6 | CONCLUSION

While the COVID-19 pandemic continues without a clear end, continuing to optimize health and recovery is important for individuals living with cardiovascular disease. With the closure of many CR programs, cardiovascular clients are left vulnerable because they cannot access resources that support their health. Without this support, they are at an increased risk of acute cardiovascular events. Home-based CR provides a solution to ensure individuals continue to receive appropriate care, especially during physically and mentally difficult times. Through advocacy and innovation, healthcare providers and health leaders can utilize new and existing strategies to meet the current challenge of delivering this important component of rehabilitation. Through careful collaboration and planning, CR programs can continue their essential work during the COVID-19 pandemic while also addressing many inequities present pre-pandemic, developing a solution for years to come.

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COMMENTARY
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COVID-19, Social Media, and Policy: Suggestions for Canada's Health Messaging Response

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ABSTRACT

COVID-19 has impacted the lives of many Canadians physically, emotionally, and financially. This commentary focuses on suggestions on how to use social media platforms to target Canadians to promote public COVID-19 related health messaging. Policy strategies that limit the use of algorithms for social media in an effort to eliminate opinion silos and provide users with a more well-rounded view of current events are explored.

KEYWORDS
Social Media, COVID-19, Pandemic, Health Messaging, Policy

1 | INTRODUCTION

The COVID-19 pandemic has forced many to adapt to new circumstances. For students and teachers, this has meant learning how to effectively utilize technology as their sole method of interaction. (1) For those employed prior to the pandemic: being laid off with little idea of what their financial future holds. (2) For those fortunate enough to still have their jobs: how to work from home. (3) Finally, for those making decisions at a public health and governing level: how to deal with the pandemic from a health, financial, and political standpoint, and how to disseminate public health messages effectively to their citizens. These are just a few examples of the mental, physical, and financial impacts of the pandemic. (2,4) Given the morbidity and mortality risks of COVID-19, public messaging reaching Canadians must provide accurate and reliable health messages that are in line with expert opinion. (4,5) This commentary reviews various ways in which health messages can be conveyed,

and proposes new health messaging strategies that can be utilized to effectively reach Canadians.

2 | HEALTH MESSAGING

Health messaging can take multiple forms. It includes top-down dissemination of health information from physicians and public health officials as well as word-of-mouth communication between family members, friends, and colleagues. It is important that all public health messages align and are consistent to avoid confusion. This is particularly true given the serious risks associated with contracting and spreading COVID-19. (5) Consistent, targeted, and appropriate health messaging can help individuals become familiar with and develop an affinity for its contents when repeatedly exposed to it via the "mere exposure effect." (6) Unfortunately, the mere exposure effect can also increase the tendency for individuals to believe information that is incorrect or false. (7) This is an issue as "fake news" has been shown to spread significantly faster than accurate news on social media. (7)

Given that Internet users between the ages of 16-64 reported using social media for an average of 2.5 hours per day during 2020, it is important to discuss this in detail. (8) Fake news detracts from important public health messaging in two ways: it encourages apathy in the population, and it propagates conspiracy theories. (7,9,10) For example, many people believe that COVID-19 only affects the elderly as they are at much higher risk of fatality from exposure to the virus. (11) Although mortality rates from COVID-19 are low amongst younger individuals, adverse complications due to morbidity remain relevant within this cohort. (12) When modeling high quality years of life lost if infected by COVID-19 (using chronic fatigue syndrome as a proxy for COVID-19's disability), one study found that individuals in their 20's can lose up to six years depending on the severity of their COVID-19 symptoms and gender. (12) Health messaging that mentions more relevant morbidity risk from COVID-19 may help combat apathy towards public health regulations in younger cohorts.

The rapid transmission of "fake news" through social media combined with COVID-19's negative impact on mental health may have promoted the adoption of conspiracy theories and movements such as the "anti-mask" movement. (4,13,14) Chen et al. surveyed healthcare workers and found that belief in COVID-19 conspiracy theories was correlated to poorer mental health. (13) These types of movements can counter accurate public health messaging and can further spread inaccurate information through both from the ground up (e.g., to family and friends) or top-down (e.g., creating a viral social media post). Disseminating accurate health information not only requires targeting the appropriate audience with the appropriate medium and message, but also combatting the spread of false information on the web and beyond. To help health expert opinion battle false news online, creation of engaging material in abundance is necessary. (9) Working together with individuals who are well-versed in creating this sort of content allows experts to disseminate this information in a way that is digestible to the masses.

3 | COLLABORATION WITH INFLUENCERS

Research has demonstrated that influential leaders within groups can promote positive health behaviours. (15,16) Campbell et al., showed that training school-aged peer leaders — voted as leaders by classmates — on the negative impacts of smoking decreased the number of individuals who engaged in smoking compared to groups without these leaders. (15) Kelly et al. showed similar significant findings when popular homosexual men were selected as peer leaders and trained on HIV prevention strategies such as using condoms and avoiding unprotected anal sex. (16) They found that individuals who had access to these peer leaders demonstrated a significant increase in condom use during anal intercourse, and a significant decrease in the frequency of unprotected anal intercourse. (16)

Collaboration with social media influencers may provide a cost-effective and targeted strategy to spread

health messaging, especially to the younger demographic. (17,18) A survey in 2020 showed that more than 90% of Canadian adults with Internet access also have access to one or more social media accounts. (18) Younger individuals (18-24) have the highest reported social media usage, making it an ideal medium to target younger cohorts. (18) A 2017 survey conducted on more than 4,000 individuals indicated that most users who followed influencers favoured those with a "lifestyle" brand, and that one third bought a service or product that an influencer was promoting. (19) Given the content that lifestyle brands produce, working with this group of influencers allows public health messages to be disseminated naturally to a lay audience.

Surveys in Canada have shown that younger people are less likely to abide by public health messaging. (17) Promotion of public health messaging may be able to encourage improved public safety if influencers collaborate with health regions, but are given sufficient autonomy to offer authentic and personalized content as these factors have been shown to foster trust. (19) The Fraser Health Region in British Columbia recruited volunteers between the ages of 20-29 to share ideas and social media content as "health influencers" to help stop the spread of COVID-19. (20) Recruiting willing individuals to create and share content can aid public health messaging, but collaborating with larger influential content creators who already have a dedicated following should also be considered. Different influencers and social media platforms target different users, and thus various combinations could be used to encapsulate a variety of demographics. (18) Creation of incentives and challenges to promote public health messaging should also be considered to encourage discourse on public health messages.

4 | SOCIAL MEDIA CONTESTS AND CHALLENGES

With many Canadians active on social media, using best practices to reach the highest number of users as cheaply as possible would help to disseminate public health messaging. (18) One issue with social media platforms is that they have varying levels of organic reach, or the ability to reach their followers without paying the company to promote their posts. (21) There are ways, however, to maximize the organic reach of a post. Promoting user engagement with a post is one method on Facebook. (21) For example, by offering an incentive like a draw for a free product to a certain number of individuals who engage with a post by "liking", "commenting", and "following" the respective public health agency on their social media feed. Contests like this serve two purposes: they increase exposure and followers to proper public health accounts, and they increase the organic reach of each post to share important public health information. When an individual has engaged with a post on their feed, their network is also able to see that activity on their feed, which quickly allows these messages to reach a wider audience across different social media platforms. When creating messaging for these contests it is important to include topics that encourage dialogue and comments on the comments of others such as: "comment below something that you are doing to keep up your mental health." This strategy will garner more engagement on posts and serves as another method to increase exposure to accurate public health channels and information. (21) Combining these methods with the right amount of paid sponsorship will help posts reach more individuals and do so cost-effectively. All contest metrics can be tracked (i.e., engagement, costs, etc.) and modulated from one contest to another to compare different messaging, demographics, and cost efficiency.

Another effective strategy is the use of health messaging challenges to engage with friends and spread health messaging. These challenges create a personalized, fun, and user-generated method to share health messaging. One of the most notable health messaging challenges was the Amyotrophic Lateral Sclerosis (ALS) ice bucket challenge (IBC) in 2014. This challenge went viral and led to a 35-fold increase in donations for ALS charities compared to the previous year. (22) Furthermore, Twitter posts during this same time period showed an increased use of the hashtags icebucketchal-

lenge and ALS also experienced a much greater usage, whereas the use of multiple sclerosis (MS) hashtags remained fairly consistent. (22) Creating health challenges similar to the IBC promotes conversations regarding the contest and its message. (19)

Creating similar challenges related to COVID-19 complications relevant to younger individuals (such as the fatigue) may improve engagement with public health messaging. (11,12) For example, one challenge can be asking users to do the max amount of body weight squats they can in one minute, while also counting back from a random number by 7. Participants would do this once at the start of the day and once after staying up for 4 hours longer than they normally would. The difference in performance could serve as a proxy for how fatigue complications from COVID-19 would feel. The competitive nature of this challenge would also encourage participation from other social media users. (12)

This challenge can teach individuals directly, vicariously through watching peers on social media, and also through discussions where peers communicate their experiences with one another. As described, health messaging contests and challenges can aid in targeting Canadians with public health messaging, but ultimately policy change is required to make a more lasting impact.

5 | POLICY RECOMMENDATIONS AND SUGGESTIONS FOR SOCIAL MEDIA

Since most social media sites that Canadians use generate revenue through advertisement, showing content that is in line with a user's viewpoints is in the social media companies' best interests, but may distort a user's reality. (18,21) As mentioned, COVID-19 has had a negative impact on the mental health of many, and with mental distress being associated with conspiracy theory adoption, which can counter to accurate public health messaging. (4,13,14) Although social media may be very useful to promote public health messaging, the limitations of this strategy must be considered. There are many issues with tailoring content to make it relevant for the end user. With regards to health messaging, tailored content may distort reality for end-users and encourage confirmation bias. When an individual only sees one point of view, they may miss an opportunity to see appropriate public health messaging. Considering that individuals who are seeing the same content have similar preferences, the majority of comments can add social validity to further the individual's belief in a particular view (e.g., that COVID-19 is a hoax). (23) The second issue is the creation of information and opinion silos where individuals are encouraged to consume media deemed relevant to them by social media algorithms. The reason why this tailored delivery of content is dangerous for the end user can be explained through the Self Determination Theory (SDT). This theory asserts that an individual's motivation can be affected by three pillars: competence, relatedness, and autonomy. (24) When an individual is constantly exposed to news on social media that opposes mainstream media, they may feel a sense of competency as they may feel like they know the "truth," but the majority are misinformed. When individuals choose a post to engage with and see others commenting in agreement with their beliefs, it would strengthen their feeling of autonomy and relatedness. This example illustrates why individuals may believe in conspiracy theories or false health information that run counter to public health messaging.

For these reasons, public health agencies should work with social media companies to ensure algorithms maximize exposure to a wide variety of perspectives. Creating a system that verifies the accounts of public health experts accounts may also aid users in distinguishing what sources are reputable on these platforms. As a long-term consideration, policies that limit or eliminate the use of algorithms to deliver relevant content to social media users should be implemented to further battle misinformation and promote health messaging. These policies will allow citizens to obtain more accurate information, see both sides of an argument, and help promote public health messaging. This type of policy could also assist in other avenues, such as elections at the municipal, provincial, and international level. As an initial consideration, public health officials should

encourage compassion and understanding between all Canadians as everyone has different content tailored through their social media feed. Through thoughtful discussion with peers who have opposing views, opinion silos can be broken down, which may encourage individuals to consider another point of view. Beyond policy, education on privacy and how social media platforms deliver content should be prioritized to ensure Canadians know how the algorithm of these platforms currently works.

6 | CONCLUSION

The COVID-19 pandemic has radically changed the way that Canadians communicate and consume information. The better individuals comprehend and comply with health messaging, the sooner we can return to pre-pandemic life. Both macro and micro strategies should be utilized to effectively target Canadians, focusing specifically on social media contests, collaboration with influencers, and policy to deter information silos and misinformation on social media platforms. By utilizing these strategies, public health will gain an advantage to better spread accurate public health messages to each individual and improve their chances of winning the battle against misinformation. The traditional lives Canadians experienced pre-pandemic have been engulfed into a new and everchanging digital world. As our society progresses through these strange and unprecedented times, it is vital that our public health messaging can traverse alongside our remodeling nation in order to inform, educate, and promote health to as many Canadians as possible.

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COMMENTARY
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How Should We Present the Epidemic Curve for COVID-19?

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ABSTRACT

Epidemic curves are used by decision makers and the public to infer the trajectory of the COVID-19 pandemic and to understand the appropriateness of response measures. Symptom onset date is commonly used to date incident cases on the epidemic curve in public health reports and dashboards; however, third-party trackers date cases by the date they were publicly reported by the public health authority. These two curves create very different impressions of epidemic progression. On April 1, 2020, the epidemic curve based on public reporting date for Ontario, Canada showed an accelerating epidemic, whereas the curve based on a proxy variable for symptom onset date showed a rapidly declining epidemic. This illusory downward trend is a feature of epidemic curves anchored using date variables earlier in time than the date a case was publicly reported, such as the symptom onset date. Delays between the onset of symptoms and the detection of a case by the public health authority mean that recent days will always have incomplete case data, creating a downward bias. Public reporting date is not subject to this bias and can be used to visualize real-time epidemic curves meant to inform the public and decision makers.

KEYWORDS
Epidemics, COVID-19, SARS-CoV-2, Communicable Diseases, Epidemiology

1 | INTRODUCTION

Epidemic curves are used to infer the current trajectory of the COVID-19 pandemic and to inform policy surrounding the COVID-19 response, including physical distancing measures, as well as shaping public perception of their necessity. When constructing epidemic curves, there are a variety of ways to date incident cases, such as by the symptom onset date or the date the case was publicly reported. Given the inevitable delays between when infections occur and when infections are detected and reported as cases, it is critical that the epidemic trajectory be communicated as quickly and as accurately as possible. The method selected to date incident cases for epidemic curves produced in real-time (rather than retrospectively, after the outbreak has

ended) can profoundly alter the impression of the trajectory of the epidemic. In this analysis, we will demonstrate that epidemic curves based on symptom onset date (or a proxy thereof), as commonly presented by public health authorities across the world, are affected by an optimistic bias regarding the trajectory of COVID-19. The slopes of these curves will always be biased downwards, regardless of the epidemic's true trajectory.

2 | WHAT ARE EPIDEMIC CURVES?

Epidemic curves show the trend in the incidence of a disease in a population through time (1) and are a mainstay of outbreak investigations and epidemiological analyses. A key feature of epidemic curves is that they are generally descriptive and can be constructed in numerous different ways, such as through the choices of case definition, subpopulations, or the method of dating incident cases. This contrasts with mathematical models such as the classic susceptible-infected-recovered model of Kermack and McKendrick (2), which are prescriptive, embedding assumptions and parameters regarding disease fundamentals. Epidemic curves date back to William Farr's investigation of mortality during the 1848–1849 cholera epidemic in England. (3) Epidemic curves may provide clues about the characteristics of novel diseases. For example, the epidemic curve of the previously unknown Legionnaires' disease showed cases tightly clustered in time, suggesting a common environmental source. This source was ultimately identified as the air conditioning of the hotel hosting the Pennsylvania American Legion convention. (4)

Epidemic curves have attained newfound prominence during the COVID-19 pandemic. Early public health messaging focused on "flattening the curve"—referring to the epidemic curve—so that the daily number of new infections did not overwhelm the capacity of the healthcare system. (5) More recently, epidemic curves have been used to guide decision makers in the further loosening or tightening of restrictions and to monitor the effects of these decisions on the trajectories of localized epidemics. Consequently, representations of the epidemic curve are prominent in public health and media reports and dashboards. (6–10) This fact makes the manner in which these curves are presented to the public all the more important.

The ideal epidemic curve would plot incident cases of disease based on the date of infection (on the x-axis), as this represents the true epidemiology of an infectious disease. However, date of infection is rarely known with certainty and is not available in real time, as the case must first be identified by public health authorities. Thus, in practice, dates following the date of infection are used to date incident cases. These dates include symptom onset date, sample collection date, laboratory testing date, and public reporting date.

Public health authorities commonly publish real-time epidemic curves using the date of symptom onset, with the logic that it is the closest measurable date to the date of infection (e.g., the Public Health Agency of Canada in their daily epidemiology update (6)). Third-party trackers such as those run by Johns Hopkins University (8), The COVID-19 Tracking Project (11), and the COVID-19 Canada Open Data Working Group (12) primarily use public reporting date, in part because more detailed date variables are not always available. These two dating methods produce very different epidemic curves, which can strongly affect the perceived trajectory of COVID-19 cases for reasons that will be explored in the subsequent section.

3 | WHY DOES THE CHOICE OF EPIDEMIC CURVE MATTER?

Public health surveillance systems are continuously updated as new information becomes available. A case is entered into the system after the public health authority receives the result from the laboratory, after which a case investigation begins, and the data are publicly reported. Over the subsequent hours, days, and weeks, additional information may be entered and previous information may be revised. These revisions may include the date the individual developed symptoms, if at all.

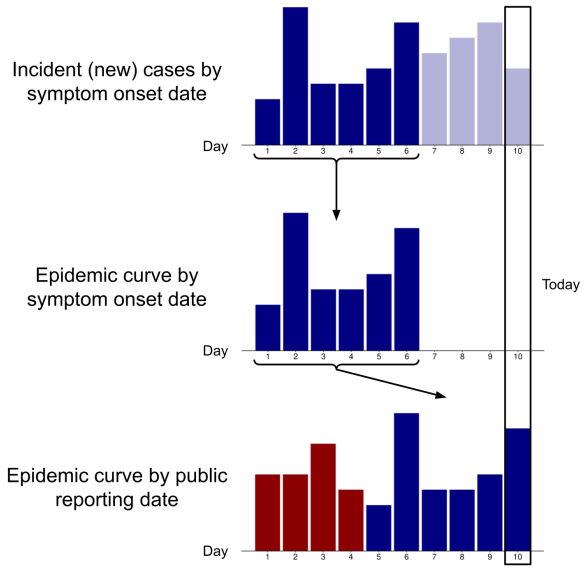

FIGURE 1 Simple illustration of epidemic curves plotted by symptom onset date and public reporting date, assuming a fixed 4-day delay between symptom onset and case identification.

Transparent blue bars indicate symptomatic cases that have not yet been identified; red bars indicate cases that became symptomatic prior to day 1. Day 10 represents the present date.

3.1 | The Illusory Downward Trend

Real-time epidemic curves based on symptom onset date are subject to an illusory downward trend in the days closest to the present day. The cause of this trend is delayed reporting: cases detected today will usually have symptom onset dates days or even weeks prior to the current date. As a result, recent days will always have incomplete case data, creating an ever-present but illusory downward trend. A simple illustration of this phenomenon is shown in **Figure 1**, which assumes a fixed 4-day delay between symptom onset and case identification. The most recent 4 days on the epidemic curve plotted by symptom onset date have no cases because these cases have not yet been identified. This artifact does not occur when plotting by public reporting date because cases are added to the curve on the date they are identified by the public health authority.

This illusory trend is exacerbated by delays in administering tests, processing tests, and communicating test results to public health authorities, since the symptom onset date will be proportionately further back in time relative to the date the case is identified by the public health authority. Consequently, a region overwhelmed by new cases will see an even more pronounced downward bias. However, this bias is not solely a technical issue but also an issue of natural history, human behaviour, and healthcare systems. Consider the following scenario: tests are processed instantaneously at the time of collection, results are immediately transmitted to the public health surveillance system, and symptom onset date is ascertained perfectly in real time. Epidemic curves based on symptom onset date would still show an illusory downward trend because of inevitable delays and variability between when an individual first experiences symptoms and when they seek and receive a test.

Symptom onset date has other practical limitations for constructing real-time epidemic curves due to delays and difficulties in the determination of symptom onset. Delays can occur because it may take several days to conclude a case investigation (particularly during periods of high case load). (13) Recall issues and patient incapacitation or death also complicate measurement. For asymptomatic cases, a symptom onset date cannot be assigned at all.

3.2 | An Example Using Epidemic Data from Ontario, Canada

To circumvent the issues inherent to measuring the date of symptom onset, public health surveillance systems in Canada generally use a proxy variable for this date called the “episode date”. If the symptom onset date is absent, the episode date is defined as the earliest available date in the following hierarchy: specimen collection date, laboratory testing date, and the date that the public health authority received the report from the laboratory. (14) Unless the earliest date (either symptom onset date or sample collection date, if the former cannot be ascertained) is the same as the date that the case is publicly reported, all cases will appear on the epidemic curve on a date that is earlier than the date on which they were publicly reported. During the early pandemic period in Ontario, the date of symptom onset was generally the

last date entered into the system (if it was entered at all). As a result, newer cases would be progressively pushed back to earlier dates on the epidemic curve as the episode date was updated, culminating with the true symptom onset date (if it could be ascertained). This process led to more recent days on the epidemic curve having fewer cases—creating the illusory downward trend.

Consider **Figure 2** which displays epidemic curves for COVID-19 in Ontario, Canada from March 1, 2020 to April 1, 2020 plotted by different date variables: episode date (the proxy for symptom onset date) and public reporting date. The three curves for each date variable correspond to datasets extracted on three different dates: April 1 (pink, the real-time dataset), April 8 (green, 1 week later) and May 20 (blue, 7 weeks later, after which edits to cases from March have largely ceased). The real-time dataset contains 2,793 cumulative cases from January to April 1. However, the cumulative number of cases up to April 1 in the May 20 data extract differs greatly according to which variable is used to date cases. Using public reporting date, the cumulative number of cases is 2,772, nearly unchanged from the real-time dataset. This is expected because cases dated by public reporting date should only change to correct data entry errors and to remove duplicates and individuals no longer meeting the case definition. In contrast, the number of cumulative cases by episode date in this data extract is 5,922, more than double that of the real-time

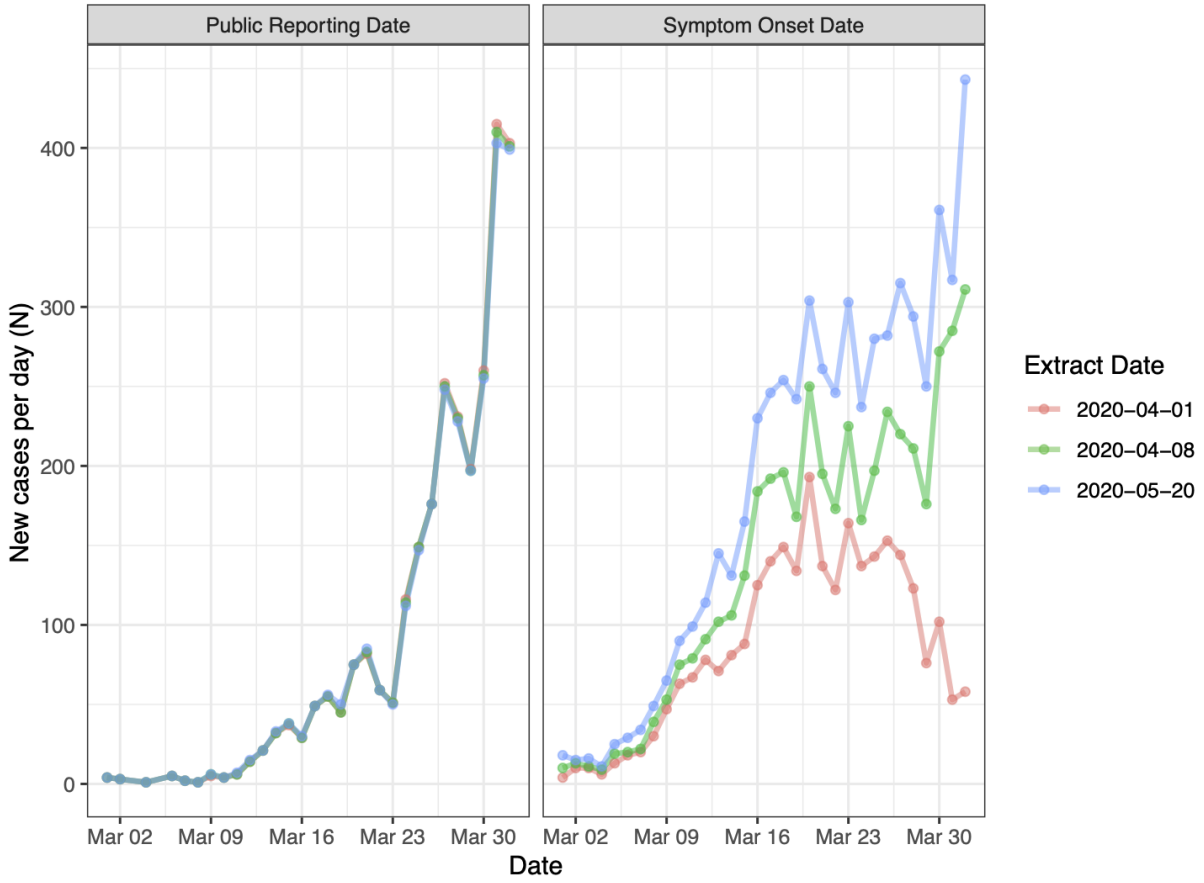

FIGURE 2 Different views of epidemic data for COVID-19 in Ontario, Canada for March 1, 2020 to April 1, 2020 plotted by episode date (left) and public reporting date (right) using three datasets extracted between April 1 and May 20.

The pink curve represents the real-time epidemic curve, while the green and blue curves are those observed 1 and 7 weeks later, respectively. Note that "public reporting date" in this figure refers to the date the case was entered into the provincial surveillance system.

dataset. This is because the real-time dataset is highly incomplete: many cases reported at the end of March had symptom onset dates in mid-March, and most cases with symptom onset dates in late March were not identified and reported until April.

The real-time epidemic curve that is plotted by symptom onset date shows a pronounced illusory downward trend. This artifact creates the impression that incidence peaked in mid-March and is rapidly declining toward the end of the month. The later data extracts correct this optimistic bias: daily incidence was climbing throughout the entire month of March. On the other hand, the real-time epidemic curve based on public reporting date reliably communicated the trend of increasing incidence throughout the month of March.

4 | HOW ARE EPIDEMIC CURVES BEING USED DURING COVID-19?

Epidemic curves for COVID-19 that are based on symptom onset date (or a proxy thereof) are commonly included in reports and dashboards produced by public health organizations around the globe. (6,9,15–20) In these figures, caveats are often given in the form of a shaded area on the graph covering recent dates, with text indicating that recent cases may not yet be reported.

When epidemic curves are used by decision makers and members of the public to assess disease trajectory amid an outbreak, curves plotted by symptom onset date can be misleading. This possibility is not merely theoretical: these curves have been misinterpreted by public officials to justify loosening public health measures in at least two American states, Georgia (21) and Iowa (22). This phenomenon of delayed reporting and incomplete incidence data is well known in the realms of infectious disease modelling (23,24), HIV/AIDS research (25) and of mortality statistics, where the manual coding of deaths often results in a lag before these deaths are counted in official datasets (26). This issue has also been discussed in the context of charting COVID-19 deaths. (27,28) Never has this phenomenon been so consequential as it is in our present moment.

5 | CONCLUSION

Real-time epidemic curves are useful for visualizing the trajectory of the COVID-19 pandemic. Epidemic curves based on symptom onset date are important for understanding the epidemiology of an outbreak in retrospect because they form an approximation of the infection curve. However, reporting delays mean that the most recent days of data on an epidemic curve plotted by symptom onset date will always be incomplete, and this creates an illusory trend of falling case numbers. This artifact limits the usefulness of epidemic curves by symptom onset date for communicating the disease trajectory in real time. In contrast, curves that are constructed using the date a case was publicly reported do not suffer from this distortion.

The COVID-19 pandemic is not over. As the virus continues to sweep across the globe and many regions experience persistently high caseloads, it is essential that epidemic curves reliably communicate the present trajectory of detected cases. The public reporting date can be used to visualize real-time epidemic curves meant to inform the public and decision makers.

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COMMENTARY
McGill Journal of Medicine

Rethinking Modern Hospital Architecture Through COVID-19

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ABSTRACT

Lately, the premier ateliers of contemporary architecture – such as Herzog de Meuron, or the Office of Metropolitan Architecture – are showing increasing interest in hospital design, once the realm of highly specialized architectural firms. This trend towards reevaluating hospital design and architecture is most opportune, as the COVID-19 pandemic urges us all to rethink the ways in which our healthcare institutions can be better designed. This commentary is a discussion on the emerging issues of contemporary hospital architecture, especially as reinforced by the pandemic. For instance, while hospital architecture today focuses on individualized care, providing each patient with hotel-like rooms, the pandemic has reminded us of the issue of capacity and inequality in these limited and costly spaces. To what extent should hospitals be centralized or decentralized? Specialized or despecialized? This commentary discusses how COVID-19 has provided insight into some of contemporary hospital architecture's greatest problems; specifically, it argues that the hospital of the future must exist on a more decentralized platform, both physically and digitally, and be more flexible in function.

KEYWORDS
Hospital, COVID-19, Architecture, Design.

1 | INTRODUCTION

In May 2021, the Venice Biennale – the world's preeminent art and architecture exhibition – premiered a short film titled "The Hospital of the Future". Created by architect Rem Koolhaas' Office of Metropolitan Architecture (OMA), the film summarized the results of OMA's team-led research on hospital architectural paradigms, inspired by their recent commission to design hospitals in France and Qatar. (1,2) A month prior, Christine Binswanger, a partner at Swiss architectural firm Herzog de Meuron (HdM), gave a lecture at the Massachusetts Institute of Technology , titled "The Hospital / The Allure of Complexity" that focused on elements of creative design in hospital architecture. (3) HdM is commissioned to build the new medical center for the University of California, San Francisco, as well as other hospitals in Switzerland and Denmark. (3)

Such recent interest in hospital design by premier architectural firms is a new and interesting phenomenon. Hospital architecture was often the work of highly specialized firms, (4) such as Perkins Wills or NBBJ, but the recent interest by design-centric firms demonstrates a shift in thinking. (1) Partner at OMA, Reiner de Graaf explains (1) how their recent commissions to build hospitals despite their lack of experience signals "that hospital design needs to be rethought". All this is in timely accordance with the SARS CoV-2 (COVID-19) pandemic, ongoing since 2019, (5), which has demonstrated the failure of healthcare facilities across the world to meet demand in times of crisis (6-9) and has inspired a need to evaluate better designs and concepts for hospital architecture.

This commentary focuses primarily on the evolution of hospital architecture in Canada and the United States. In such countries, contemporary hospital architectural paradigms are centered on individualism, decentralization, and specialization. Decentralization (10) refers to the transition from the postwar "modern" hospital – marked by its grand, "hospital-as-office-tower" (4) design – to the more "postmodern" hospital of today, which is typically more low-rise (3,4) and less clearly defined as a singular institution. In this latter typology, hospitals resemble more so hotels and shopping malls than offices, wards are replaced by individual rooms, and an emphasis is placed on incorporating as much "anti-hospital" elements in its design as possible. (4,11,12) In addition, hospitals today are smaller in scale, retaining less bed capacity than their predecessors, but nonetheless more specialized in treating specific illnesses through costly expert care. (13,14) Thus, the postwar model of the "tower hospital", in all its conglomerate might and comprehensive capacity, is now an antiquity as hospitals become smaller in scale and dissolve in character and form. However, despite such typology shifts, the pandemic sheds light on the issue of capacity and inequality within these spaces. Throughout 2020, hospitals simply did not have enough bedspace and intensive care capacity to meet demands. (6-9) With space limited by the pandemic, certain demographics that already had disadvantaged access to care were unable to access treatment, causing disparities most prominent in rural areas and black communities. (15-16) The hospital itself emerged as a locus of infection, avoided by many. (17) Once again, paradigms of centralization or decentralization, and specialization or despecialization, re-emerged as the defining questions for hospital architecture and its typologies.

This commentary examines how COVID-19 has challenged or reaffirmed architectural paradigms for hospital design. Specifically, it focuses on two central issues, (1) centralization, and (2) specialization. It concludes that COVID-19 has reinforced the decentralized notion of hospital design and challenged the trend towards specialization. Accordingly, the future hospital should be decentralized throughout the city, focus less on outpatient settings, and include within its design enough "flex space" to accommodate for multiple and scalable functions.

2 | CENTRALIZATION VERSUS DECENTRALIZATION

The word hospital stems from the Latin root *hospitium*, which denotes a place to entertain strangers. (2) As such, hospitals were originally small, religious facilities used to look after the poor or homeless, while most medical services were carried out for the wealthy in their homes. (2,18) Centralization of the hospital as an institution occurred only after the advent of medical technology in the 20th century, notably the X-Ray machine, which had to be housed in a singular locus and was used by rich and poor alike. (2,19) Technology thus gave birth to the centralized hospital, marked by its "tower-like" design.

Contemporary architectural paradigms focus on decentralizing the hospital once again. This decentralization occurred at all the architectural, managerial, and city-planning levels. Early on, the hospital began to integrate with shopping malls, parks, and cafes (12) so as to disguise its true character. (20) Then, it physically dispersed throughout the city, being less concentrated in one environment and smaller in capacity. The buildings became wide rather than tall, with more elements of cre-

ative exterior and interior design. (3) In fact, it seemed that the less a hospital took the characteristics of a hospital, the better.

Reasons to decentralize the hospital are many, but there are mainly the trends toward Evidence-Based Design (EBD) and neoliberalism. EBD refers to the ways in which surrounding design may improve patient conditions and outcomes. In his milestone study that gave birth to EBD, Roger Ulrich noted how recovery of patients from cholecystectomy improved when a tree was visible out the window. (21) Further developments in EBD theory (22) in the late 20th and early 21st century provided a medical basis for changing the hospital environment from an office-like form to include more windows, green space, art, lighting, (12) and as many anti-hospital elements as possible. (20) In addition to EBD, neoliberalism, a politico-economic model of the 20th century in which free, autonomous markets are fundamental, (23) also played a role; specifically as patients, too, were construed "as consumers and responsibilised citizens". (12) As patients become autonomous economic players, the hospital adopts "features of the shopping mall, the hotel and the home", (12) so as to provide as much consumer freedom to patients as possible. Today, one can easily see the ramifications of these shifts: from the Alberta Children's Hospital in Calgary – with its mango-colored walls and a mall-like atrium – to the McGill University Health Centre in Montreal, whose design is based on shopping malls, parks, and suburbs, and features within its campus a Zen Garden. (4)

At the physical, city-planning level, the popular opinion from contemporary architectural theorists is that the hospital of the future will be integrated into cities. In their most extreme form, "hospitals will be everywhere". (1) The hospital will be "the city in itself, an urban condition", as stated by Reiner de Graaf at OMA (1). Binswanger of HdM (3) also expresses similar theses guiding contemporary hospital architecture, asking: "Are hospitals cities or organs of cities? How do we deghettoize hospitals?". What was once a grand office tower is now a scattered array of boutique clinics, as the singular hospital decentralizes into smaller entities embedded throughout the city, or even, no physical form at all.

This "hospitals will be everywhere" concept is in fact strengthened by recent advancements in digital communication, specifically in remote treatment. In telemedicine, patients no longer need to visit the doctor in person, but can easily communicate with their physicians online, antiquating the singular existence of the hospital. In McKinsey's report titled "Hospital Care in 2030", (24) there is even discussion of iPhones conducting blood tests at home, and the elimination of outpatient waiting rooms entirely. Recent advancements in telemedical technology has made possible not merely remote consultation, but remote diagnosis and post-treatment follow-ups. (25) As such, patients of the future may not often visit the hospital, but rather do so remotely or via smaller institutions across cities. (24)

COVID-19 supported the argument for decentralization through its encouragement of telemedicine. Throughout the pandemic, patients who otherwise could not access the hospital resorted to receiving consultation online. In the United States, telemedicine is already a market worth $250 billion, (26) with more than 50% of American healthcare consumers registered in 2020. (27) Though most were forced into using telemedicine during COVID, an Accenture survey (28) found that 60% of respondents wanted to keep using telemedicine even after the pandemic. People generally found treatment at home more comforting than treatment at the hospital, (28) which corroborates the results of a study in pediatric emergencies which found that telemedicine was more beneficial for patient recovery. (29) Moreover, this trend was not unique to the United States; even in Bangladesh, where the issue of medical deserts and rural medicine is most pressing, telecare was a promising platform to combat COVID-19 and enjoyed by many. (27) It is important to note here that this commentary focuses primarily on urban environments, thus overlooking the important issue of rural medicine and medical deserts, (30,31) which architecture must also address. But in any case, COVID-19 promoted telemedicine as a potential paradigm for the hospital of the future in its completely decentralized state.

The recent pandemic also heightened public worry

about consolidated hospital structures and their potentials for mass hospital-acquired infection. COVID-19 engendered a fear of centralized spaces, like hospitals, at which people congregate and infection occurs. Richterman et al. noted (17) how "early case series in China estimated that 44% of 179 severe acute respiratory syndrome [Covid-19] infections were hospital acquired", proving the public health threat of the centralized hospital during a pandemic. This threat then translated into a public fear of the hospital, avoided even by people who were critically ill and required treatment. (32) Healthcare workers themselves were also fearful of the environment. (33) Ultimately, the centralized hospital has been labelled a threat, garnering support for the decentralized form of the hospital. Perhaps the most effective way to minimize hospital-acquired infection is to not have a physical hospital at all. Decentralizing the hospital seems to provide a solution even for the problem of inequality during COVID-19. Black and indigenous communities, in particular, have suffered disproportionate impact from COVID-19, especially due to their lack of access to medical services in "trauma deserts". (15,16) Indeed, in the United States, "Black and Hispanic individuals faced the greatest exposure to overburdened ICUs" as one federal research found. (34) To decentralize the hospital, either through telemedicine or physically throughout the city, would potentially be a democratizing force for healthcare and help to alleviate this inequality. Of course, the problem of disparity is not as simple as proximity to medical services, but rather includes a myriad of public policy quandaries. Architecture must work with public policy and city planning to create solutions for health inequality as reinforced by the design of healthcare institutions.

Architecture must reflect this growing trend towards remote medicine and decentralized hospital spaces by scaling back spaces for outpatient care. As centralized hospitals themselves become a threat , being spaces of infection and undemocratic access , telemedicine seems to be a promising alternative. Thus, the hospital as a space for outpatient consultation is now exchanged with digital platforms. Architects must claim the hospital as a space of inpatient care and necessary high demand functions (i.e. critical care, operations and procedures, and emergency responses), whilst minimizing spaces for routine outpatient visits. The hospital will be less so a place to consult, but a place to operate; as the McKinsey report explains, (24) the picture of the outpatient sector with chairs and waiting lists is outdated. In essence, COVID-19 has provided more momentum to the effort of hospital decentralization, and one can expect to see this trend translated architecturally.

3 | SPECIALIZATION VERSUS DE-SPECIALIZATION

Another trend in hospital architecture is that instead of general hospitals, highly specialized "clinics" have become mainstream. (13) This trend is expected: As the decentralized postmodern hospital grows smaller and wards are individualized, the focus for hospital strategy moves from comprehensive capacity to expertise care for a few patients with specific conditions. Indeed, the portfolios of the aforementioned architectural firms list mostly small clinics with a boutique-design for specific conditions; such as REHAB Basel, a specialized neurorehabilitation center by HdM, with only 100 beds. (3)

The factors facilitating this trend are mainly changing patient expectations and economic advantage. As explained in a report by McKinsey titled "The Hospital is Dead, Long Live the Hospital", (14) patients today "have higher expectations than before" as therapy for major illnesses becomes more targeted and personalized. "High-quality care requires concentration into specialised, high-volume centers of excellence", (14) however such expertise is not possible in a general hospital's economy of scale. (13) Foreshadowed by the effect of neoliberalism in healthcare as explained earlier, (12) there also exists the profit motive: specialty hospitals – especially in the cardiac, orthopedic, and surgical fields – draw in more financially wealthy and profitable patients, while fueling competition and threatening the survival of safety-net general hospitals. (35,36)

The case for specialized hospitals, however, was not supported by the pandemic; if anything, the importance

of the general hospital was reinforced. The pandemic reminded us of the limited function and capacity of specialty hospitals: they are unable to adapt to crisis situations and are an unaffordable model of care in contrast to the safety-net model of general hospitals. (356,36) In terms of capacity, today's specialized hospitals such as REHAB Basel maintain a minimum capacity usually of around a hundred, which pales in comparison to the general hospitals of the late 20th century (19) whose bed counts reached the scale of thousands. The problem is that specialty hospitals simply do not offer enough capacity and flexibility in function during crisis situations like COVID, during which lack of bedspace is a significant problem. (6-9) Of course, the problem was also a lack of medical personnel (7), in addition to bedspace, and such issues must also be addressed through proper policy.

Responses to COVID-19 also demonstrated that spaces of healthcare need not be permanent, but can be flexible in function, be built and unbuilt. Throughout the pandemic, temporary architecture developed all throughout hospitals and cities, including temporary testing centers, reception centers, vaccination centers, and such. Places conventionally far removed from healthcare – from hotels to parking lots – imaginatively repurposed themselves as "surge hospitals" throughout the world. (37) Perhaps most famously, China built and unbuilt a 1000-bed hospital in Wuhan. (38) This trend is incredibly promising to architects, who are quick to articulate the most pressing issue of hospital design: (10) With rapidly evolving technologies, hospitals face an "ever quicker expiry date of the typology". (2) The lifespan of hospitals is shrinking dramatically, and in its most extreme form, hospitals are obsolete as soon as they are complete. The main challenge for hospitals, therefore, is adaptation and flexibility, (10) and to see such flexible spaces – built and unbuilt according to contemporary demand – may be an encouraging solution.

However, as much as COVID-19 may have discredited the model, specialized hospitals are still an important adaptation mechanism to our changing patient demographic. In tandem with the paradigm of flexible spaces as demonstrated by COVID, the solution from an architectural standpoint is to create in hospitals enough "flex-space" – spaces that, in exceptional times, can be rescaled and maneuvered from its original purpose to another. With such spaces, hospitals can actively reconfigure to meet certain needs, whether it be enlarging bed capacity or building vaccination centers. Indeed, the acknowledgement of hospital spaces as flexible is not a new phenomenon, but a paradigm shift already underway. The McMaster Health Sciences Center in Ontario is one project noted for flexibility in design; revolutionary for his time, the architect "Zeidler created an infinitely flexible space, deliberately designed never to be finished", including within its design a potential to expand horizontally and vertically. (10) Recently, another major hospital development in Paris by the renowned architect Renzo Piano has attracted jury members for "the capacity for scalability", which has allowed for "the addition of hospitalization units and the capacity for resilience to exceptional health situations." (40) Such flexibility in healthcare spaces is promising as we still grapple with COVID-19, and architects must keep this flexibility into consideration to design hospitals that are scalable for both exceptional and non-exceptional times moving forward.

4 | CONCLUSION

The built environment is a function of its time. For contemporary hospital architecture, this function has meant two specific changes in typology: (1) decentralizing the postwar hospital – dissolving the once castle-like hospital into multiple, small hospitals throughout the city, and promoting the "anti-hospital" in hospital design – and (2) specializing the general hospital – replacing the hospital with the specialty clinic, which has lower capacity but a greater focus on expertise. However, the universal experience of COVID-19 has changed the ways in which we consider spaces of healthcare. Specifically, it has supported the notion of decentralized healthcare by encouraging telemedicine and labelling the consolidated hospital as a place of risk. On the other hand, it has challenged the notion of specialty hospitals by emphasizing the im-

portance of hospital capacities. Architecture needs to allow such lessons learned to be incorporated into future design.

The hospital of the future will no longer need large outpatient spaces, as many proceedings can now occur digitally. It will be highly integrated into cities, and consequently less congested as patients visit such places less frequently. It will likely remain specialized but will include within its design enough "flex space" that can be maneuvered to allow flexibility as needed. Of course, limitations exist in such policy recommendations: there are opportunity costs involved with allocating space, capital, and money for flexible functions in hospitals and with purposefully moving more outpatient services online. Despite the costs, such changes would allow better preparation for exceptional times such as COVID-19, however ephemeral they may be. Therefore, as emphasized throughout the essay, architects must work with public policy and city planning sectors to accommodate for both exceptional and non-exceptional times. Only then will the hospital of the future be a readied institution, a truly postmodern place and space, suited for its time and time thereafter.

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COMMENTARY
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Engaging Pre-Clerkship and Clerkship Students as Medical Scribes in the Emergency Department

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ABSTRACT

The Emergency Department (ED) is a highly stressful and fast-paced environment in which doctors are challenged to efficiently adapt and recall knowledge to make safe patient-care decisions. This commentary discusses the benefits of exclusively hiring pre-clerkship and clerkship medical students as medical scribes in the emergency department. A total of twenty-eight (28) articles and studies are explored and used to reflect upon the benefits of scribing implementation in medical education. These include, but are not limited to, increasing medical student exposure to the specialty of emergency medicine, enhancing their clinical skills, and assisting students to pay-down their medical school-related debt. Furthermore, appointing medical students as scribes is mutually beneficial to the ED by helping to cut down the lengthy wait times for patients and reduce the significantly high rates of emergency physician burnout. We conclude that hiring medical students as scribes in the ED is a potentially beneficial practice that merits further consideration and analysis.

KEYWORDS
pre-clerkship student, clerkship student, medical scribe, emergency department (ED), patient-doctor interaction

1 | INTRODUCTION

Physician burnout, the feeling of emotional and physical fatigue from excessive work hours, has been on the rise for many years. (1) The rise in involvement of medical scribes in the healthcare field has decreased documentation time and assisted in lowering such physician burnout. (2) A medical scribe is a trained individual

whose role is to concurrently document pertinent medical information during a patient-physician encounter. (3) Due to limited scribing positions, it is more difficult for medical students to secure clinical placements when competing against scribes in certain departments, such as the Emergency Department (ED). (2) The erratic environment, high student interest, fast-paced acute setting, and limited availability of resources have rendered the ED one of the most sought-after fields to gain experience in. (4) This article reflects on what is gleaned from the literature to support the conclusion that hiring more medical students as medical scribes can assist in tackling the multiple concerns raised.

2 | BENEFITS FOR MEDICAL STUDENTS

2.1 | Financial Benefits

Medical students are facing a huge burden due to the cost of medical education over their academic and training years, and many graduate with overwhelming amounts of debt. (5,6) The anxiety of debt amongst medical students has an adverse effect on their overall wellbeing and academic performance. (7) Debt is correlated with poor academic performance, increased stress levels, and adverse effects on mental health. (7) Finances remain the second most common contribution to stress reported by medical students, right behind coursework. (7) It is crucial to mitigate the financial burden students carry to improve their wellbeing and success in medical school.

As medical record-keeping is shifting from paperwork to computers, scribing employment is growing across North America. (8) Hiring medical students as medical scribes presents an opportunity to ease the finance-related stress. Summer and part-time scribing jobs can allow medical students to earn income while balancing their rigorous coursework. (9) However, the responsibilities of the scribing job could also add to the preexisting stress from coursework. Scribing companies also seek out medical students requiring part-time employment because they have an increased chance of training success. (8) Moreover, medical students are likely to reduce the cost and time dedicated to scribe training because of their background and experience, thus benefiting the hiring companies. (9)

2.2 | Increased Exposure to Emergency Medicine

Throughout their education, medical students require ample exposure to the emergency department, and yet, they have reported experiencing otherwise. (10,11) In a retrospective analysis, none of the 75 final-year medical students covered all the curriculum's recommended training categories. (11) Many explained that they were insufficiently exposed to patients in the emergency room, which raises the concern that medical students are not receiving adequate exposure and training in the emergency department. (11) Hiring medical students as medical scribes enables them to strengthen their skillset and enhance the quality of care, while increasing medical student exposure to the emergency department. (12,13)

As part of developing their professional abilities, medical students must train in interprofessional collaboration, enhance their communication and organizational skills, and learn to recognize patterns. (12,13) Working as a scribe will allow students to achieve this while being actively involved in the day-to-day routine of an emergency department physician. (12) In contrast to observerships and shadowing experiences, students working as medical scribes are challenged to strategically summarize the details of the patient encounter. (12,14,15) This enables them to enhance their familiarity with medical terminology and standard procedures in the emergency room. (15) Additionally, the students will experience doctor-patient and doctor-family interactions that will increase their competency in history-taking and their communication skills. (14) Therefore, medical students will gain valuable insight into emergency medicine and understand how to think like a doctor. (12)

Medical students working as medical scribes in the emergency department will serve to benefit both the

students and the medical practices in which they work. As a result, this will increase medical students' exposure to the emergency department and establish the reliability and confidence of the next generation of physicians.

3 | BENEFITS OF HAVING MEDICAL SCRIBES

3.1 | Increased Access to Medical Scribes

The use of medical scribes in hospitals has become increasingly popular over the last few years. According to the American College of Medical Scribe Specialists, the number of working medical scribes in the United States has increased from 20,000 in 2015 to a projected 100,000 by the end of 2020; roughly allowing 1 in every 9 physicians to have access to a medical scribe when practicing. (16) However, even with the drastic yearly increases in medical scribe employment, the vast majority of physicians still do not have access to a medical scribe. (16)

A major factor pertaining to why the use of medical scribes has not become ubiquitous within physician practice relates to a lack of desirability associated with medical scribing as a full-time vocation. It has been reported that medical scribes make roughly USD$15-25 per hour, work long hours, and work in an intense and stressful environment. (2,17) As such, the merits of a medical scribe job alone are often not enough to convince people to get the necessary training and commit to being a medical scribe long-term. For medical students, there are numerous subjective benefits that increase the desirability of being a medical scribe, although, it does not reduce the large rate of turnover associated with the scribing profession. (2,8)

Additionally, it has been shown that training medical students as medical scribes may be the most economically viable option. A study found that a comparison of 3 groups of students (medical students, pre-medical students, alternative background unrelated to medicine) showed medical students were the most efficient to complete the medical scribe training by a significant margin. (8)

3.2 | Reducing Emergency Department Wait Times

Studies have shown that ED overcrowding is widespread in most Canadian and American cities. (18) Lengthier wait times in the ED not only puts the patients' health at risk, but it reduces patient satisfaction and leads to overcrowding in the emergency room. (19) In a research study conducted by the Canadian Institute for Health Information (CIHI) it was demonstrated that, in 2018-2019, patients who visited the ED spent an average of 3-4 hours upon receiving their primary assessment. (20) However, 90% of these visits resulted in the patients spending up to 10.9 hours in total. (20) Hiring medical scribes in the emergency department enhances patient-physician interactions, increases patient satisfaction, allows for better distribution of administrative tasks, and improves workplace flow. (14) According to Scribe America, medical scribes generate noteworthy improvements in doctors' feedback and the accuracy of the medical charts. (21) This enables the physician to assess and treat more patients in less time and increases their productivity by up to 13%. (22,23) Furthermore, a direct correlation has been observed between the implementation of medical scribes and a reduction of clinical wait times.

Medical scribes play a significant role in improving patient experience by allowing for more valuable clinician interaction with patients and resulting in more accurate and organized patient records. (14) Thus, the implementation of medical students as medical scribes would considerably reduce the stress and workload of the fast-paced environment of the emergency department on physicians, while potentially reducing wait times.

3.3 | Relieving Overworked Emergency Care Physicians

The rise of clerical burden is a major driving force for the increased emergency department physician burnout rate. (24) Causal of this trend is the transition towards Electronic Medical Records (EMR), that can provide clinicians with flexibility at work but add to the continuous

number of hours of work past their shift. (24) The introduction of EMR without creating space to preserve the energy of those who manage the medical system leads to increased physician burnout, as well as a drop in both productivity and patient satisfaction. (24) EMR requires efficient navigating skills in addition to the other skills that physicians have to acquire proficiency in as a part of their training. (25) Moreover, EMR are prone to failure (system crash, errors at entry in medication lists, and examination findings) resulting in an additional stressor in the ED. (9,24) Many physicians have agreed that the integration of medical scribes into the medical team alleviates work stress as it allows them to focus on patient interaction and increases patient satisfaction. (12) With the decline in physicians' energy, efficiency, and overall mental health, the introduction of medical scribes reduces the burden on physicians created by EMR documentation. (12,24)

When medical students are given the opportunity to aid physicians by scribing, they acquire the logic of medical decision-making due to the exposure to different scenarios and makes pattern recognition become second nature. (12) Furthermore, using EMR repetitively in medical practice allows medical students to recognize incidents of miscommunication and learn where mistakes can happen in order to prevent them in the future. (12) Medical student scribing also provides an opportunity for mentorship of students who will later lead the medical field, and through this relationship, students can learn effective patient-physician communication and build their clinical style. (12) Making use of medical student scribes is a measure of clinical care redesign that is mutually beneficial for both parties.

4 | CHALLENGES OF IMPLEMENTING SCRIBES IN THE EMERGENCY DEPARTMENT

While healthcare systems are rapidly hiring scribes for licensed clinicians as a means of potentially decreasing physician burnout and patient documentation time, this can introduce certain complications to those aspiring to become successful MD candidates. (2,24,26) The main reason behind overcrowding in the ED is due to too many patients being admitted, and thus, scribing could potentially have a very little effect on the wait times.

Increasing prevalence of scribes in hospitals and private clinics might lead to the rise of overall competitiveness of medical school applications. (2,24) For instance, medical scribing in the US is quickly becoming the norm for many pre-medical applicants and is strongly suggested by various medical school admission committees. (2) To enroll as a scribe in the United States, students are required to either complete a minimum of 120 hours of clinical training or partake in 40-hour courses containing EMR modules. (2,26) Given those requirements, the majority of clinicians prefer hiring scribes who are going to be willing to work with them full-time for a minimum period of 6-12 months, which will present challenges to pre-medical and medical students due to lack of time, commitment, as well as inability to handle such hefty responsibilities while carrying out their primary role as a medical student. (2,9)

Additionally, most medical schools prefer choosing applicants who have strong exposure to medical and clinical settings prior to enrollment in their programs. (2,9) The increased exposure that some applicants will have with scribing experience may lead to higher expectations and admission barriers for future applicants. (2,9,24) Scribing would also emerge as a perceived benefit or even be considered as a "hidden pre-requisite" that can eventually blend in with medical school application. (2,9,24) It is important to prevent introducing unintended consequences of hiring students as scribes. It is not the goal to deter students from applying for scribe occupations, but to rather avoid unintentional consequences of scribing experience from evolving into a "hidden pre-requisite". (2,9,24)

A pilot study showed that hospitals' grants paid the scribes in Canada, whereas in the US, the scribes are paid by the physicians, although it may vary depending on location. (27) In other public scribing models, such as Australia, students reported that they benefited from the experience and complemented their medical school education. (28) Whereas the US-based scribing models

focus more on the financial aspect of benefits. (28) The benefits of scribes are transferable in both public and private healthcare systems; however, more research is needed to examine different scribing models and how they are funded. (27)

5 | CONCLUSION

Through this commentary, we reflect on what is gleaned from the literature to support the conclusion that hiring more medical students as medical scribes can assist in tackling long wait times in the ED and physician burnout. Although such initiatives can begin tackling these aforementioned concerns, a collaborative effort is required across faculties to implement scribing programs to ensure medical students can gain financial and educational benefits. Considering the diverse healthcare models and funding systems in different countries, this may prove to be a challenge to implement. Having said that, the benefits of supporting students financially, increasing exposure to the field of emergency medicine, supporting attending physicians, and decreasing patient wait times are all possibilities worth exploring with further studies and initiatives.

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COMMENTARY
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Rewarding Progress: Effective Learning Strategies Through a Variable Ratio Incentive-Based Approach in Medical Education

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ABSTRACT

Medical students are faced with many unprecedented challenges, one of which is the large amount of material they are required to learn and retain. While effective learning strategies have been thoroughly researched, stress levels amongst medical students remain very high due to perceived failure to retain material, suggesting that novel methods of implementing such existing strategies are required. Aside from stress levels, additional challenges in medical education include the incorporation of inconsistent testing methods and the challenge of accommodating different learning styles and preferences. A more evidence-based approach that aims to cover many learning styles at once may be desirable. The aim of this commentary is to present some of the current learning and teaching strategies utilized within medical education across the world and to promote a novel supplementary approach to medical education involving a variable ratio incentive-based system of active recall and spaced repetition. This system aims to reward small achievements throughout the semester and complements formal structured examinations in order to motivate students. While this model has yet to be tested, we hope to motivate medical faculty to pilot a program with these evidence-based strategies in mind.

KEYWORDS
active recall, medical education, spaced repetition, variable ratio reinforcement schedule

1 | INTRODUCTION

The traditional medical curriculum offered in North America typically consists of two years of lecture-based science acquisition (termed pre-clerkship years) followed by two years of clinic-based application (termed clerkship years) (1). Although this structure has been repeatedly shown to prepare medical students success-

fully for a career in healthcare, the curriculum, specifically the lecture-based pre-clerkship years, may consist of learning objectives too copious and too advanced to truly benefit medical students at the introductory level. (2) To combat this, there has been a trend to transition from traditional lecture-based approaches to practical problem-based learning which combines basic science knowledge with clinical skill development. (3) In addition, medical schools have taken the initiative to study and implement flipped classroom teaching methodologies in which students are given the time to independently explore study topics before group sessions. (4) This method uniquely features the student as a leader; meanwhile, the instructor acts as a facilitator rather than an educator. This movement towards a student-centered approach is ideal because it adequately prepares students for real-life situations that they will face throughout their medical career. (2) The aim of this commentary is to present some of the current learning and teaching strategies utilized within medical education across the world and to present a novel supplementary approach to medical education involving a variable ratio (VR) incentive-based system of active recall (AR) and spaced repetition (SR). This paper introduces a recommendation to supplement already existing study and testing techniques utilized by medical schools. Although it has not yet been tested, the aim is to inspire medical school administrations to pilot a program that incorporates such study techniques in order to provide experimental evidence to compare with the supporting theoretical data.

1.1 | Challenges Faced by Medical Students

Despite numerous advancements in education, medical students are still presented with an overwhelming volume of material that they must comprehend and retain. Moreover, physicians are life-long learners; as such, their medical education should serve as the backbone on which continued learning stands. (1) That being said, studies have shown that simply reading and explaining lecture content to oneself is a suboptimal and superficial learning method for long-term retention of information. (5) Increased academic demand paired with seemingly inefficient learning strategies have been shown to contribute to anxiety, feelings of inadequacy, inability to cope, self-doubt, and intellectual fraudulence which has become known in academic circles as “imposter syndrome”. (6) Difficulty coping with this stress can promote thoughts of dropping out and cause a deterioration in academic performance. (7) Even more concerning is the rates of psychological comorbidities such as depression and suicidal ideations seen among medical students. A meta-analysis of nearly 63 000 medical students internationally found that 33.5% of medical students reported feelings of depression within their first year with that number dropping slightly to 23.5% towards the end of their medical education (8). This is significantly higher than the range of 8.8-9.6% of young adults with depression reported by the Journal of the American Academy of Pediatrics (9) Also of concern is the need that medical students felt to spend the majority of their time studying and the feeling of guilt whenever they engaged in other activities during their spare time. (10) A qualitative study looking at medical students’ perception of stress found that students began compromising their health by not exercising or manipulating their sleep schedules in order to keep up with their studies. (10) Similarly, a cross-sectional study administered a questionnaire to 700 international medical students and found that nearly 50% of a medical student cohort self-reported psychological distress throughout their medical school education. (11) High levels of exhaustion are often associated with increased medical mistakes, negative attitude toward patients, burnout, and reduced likelihood of success in the healthcare field. (12, 13)

2 | CURRENT TESTING METHODS

Many different testing methods are currently being utilized by medical schools across the world. Some of these methods include but are not limited to essay style questions, multiple choice exams, group projects, matching

items, case assessments and Objective Structured Clinical Exams (OSCE). (14) It has been suggested that there are important factors for faculties to consider prior to choosing which method would work best for their cohorts such as what material is to be assessed, the reason behind the assessment, and the validity and reliability of such methods. (14) For example, although patient management problems, which stimulates a clinical environment, asks students to pick the appropriate solution and provides them with the results of the action they select, seem to be heavily relied upon by medical schools as the preferred testing styles, they have been shown to lack face validity. (15) In fact, utilizing a method such as multiple-choice questions yielded better outcomes for students, with better reliability and validity in practice. (15) In addition, even within multiple choice testing, the number of choices has been a topic of discussion and multiple papers have proposed different ideas for the optimal number of selections. (15) Furthermore, extended discussions have also taken place with regards to implementing open-ended questions in written summative assessments, in which a definitive conclusion about its use was difficult to make. (16) On the other hand, a literature review assessing study strategies found that medical students who engage in self-directed retrieval methods with spaced repetition perform better on formal examinations that assess clinical knowledge. (17) Another study recruited 72 medical students to complete a survey regarding study strategies which showed the benefits of retrieval practice in a classroom setting and illustrated advantages of utilizing many spaced repetition initiatives. (18) While there has not been a consensus on the best testing methods for medical schools, it appears that some strategies have shown more promising outcomes than others.

2.1 | Current Studying Techniques

Medical school students must commit long hours to understand, retain, and apply the large amount of information which is taught throughout their education. (19) Although each student differs in their approach to learning, there are several common trends in the study techniques utilized by medical students around the world. According to a study investigating medical students' study habits, the overwhelming majority of students (77%) utilized self-made summary notes based on lecture material which they then committed to memory. (20) Others utilized a slightly more advanced learning strategy by designing charts, tables and flow-charts into their notes. However, only 27% of participants used evidence-based active learning strategies. (20) A study method that is gaining much traction is Anki – an open-source program designed to reinforce concepts by implementing knowledge retrieval via flashcards. Anki is designed to allow students to self-assess their knowledge (i.e., if they feel the concept to be "easy", it will not be tested for a longer duration than a concept that is deemed "hard"). A literature review study conducted in the United States showed that students who self-test in preparation for exams often use traditional multiple-choice strategies while only 31% of students used Anki as a preparation tool, despite being associated with higher scores on formal examinations. (17) Another successful study strategy, albeit uncommon, is by utilizing case-based learning. This was shown to be positively correlated with exam results in a medical student cohort during their emergency psychiatry learning section. (21) Although studies have shown the advancement of students towards evidence-based learning strategies such as active recall and spaced repetition (22), a significant portion of students remain dedicated to the traditional methods of studying.

2.2 | Barriers to Change in Medical Education

The many challenges that medical students face are not foreign to medical school faculty. However, implementing new learning strategies has proved challenging due to a lack of resources and limited time. (23) A great deal of consideration must be taken prior to making changes in a medical school curriculum to ensure it appropriately accommodates for the students' needs. Implementation of new curricula would require constant evaluation by faculty members, frequent communica-

tion and feedback between faculty and students, training support to faculty members, an evaluated reward structure, and prevention of a drop in the students' performance as they adapt to a new strategy. (23) Even after these changes are made, ensuring smooth implementation and efficiency of a novel approach is a time-consuming and resource-consuming endeavour. (5)

3 | EVIDENCE BASED LEARNING STRATEGIES

Although many studies have thoroughly investigated evidence-based learning methods, some proven learning strategies are not a standard component of current medical education. (24) One such strategy is Active Recall (AR), in which a student is prompted to recall information through techniques such as flashcards. This has been repeatedly proven to be superior to recognition strategies such as those utilized by multiple choice style questions. (25) In fact, even If students fail to correctly answer a question, active recall learning strategies have been shown to optimize retention of information when compared to other strategies. (24) The second method of learning is Spaced Repetition (SR), which individualizes questions to the learner. (27) In other words, concepts with which the learner is struggling are repeated more often than concepts that have been mastered. (27) This has been shown to maximize the efficiency of study time and optimize long-term retention. (26) Additionally, expanding retrieval practice is a technique which can be combined with spaced repetition and active recall for optimal results. (26) This involves gradually increasing the time interval between testing sessions and has been proven superior to other study strategies. (27) Moreover, if students are consistently participating in such retrieval practice, the information they retain will be accurate and resistant to extinction, relative to other methods of study. (24)

3.1 | Incentivized Learning

Therefore, such methods of learning are effective for students to grasp and engage with the new content. Despite this, they are not actively used in traditional medical school curricula. (4) As such, students who may be currently applying this method of learning must do so independently, without any direct means for reinforcement or reward. There are many methods of reinforcement that motivate individuals to engage in a certain task. According to the psychology textbook, The Psychology Around Us (28), reward strategies are typically characterized into four categories: 1) Variable interval (VI) in which a response is rewarded after an unpredictable amount of time has passed. 2) Variable ratio (VR) in which a reward is given after an unpredictable number of responses. 3) Fixed Interval (FI) in which the participant is rewarded after a specific amount of time has passed. 4) Fixed ratio (FR) in which reinforcement occurs after a specific number of responses. Although constant reinforcement has proven to be successful for the early stages of learning, optimal long-term retention of information is achieved most rapidly through VR reinforcement schedules. (29) Along with being the most effective as a motivational strategy, VR has also been identified as the method that is most resistant to extinction. (28)

4 | INNOVATIVE INTEGRATIVE SOLUTION

Based on these evidence-based learning and reward strategies, we propose a system which uses an incentive-based approach to motivate students to engage in daily self-testing and recall activities. Students will be marked on completion of the activities and would receive positive reinforcements in the form of grades, delivered through a VR schedule, which will count towards their final semester marking scheme. This activity will be optional as some students may not benefit from this additional intervention as they are already optimizing their AR and SR strategies.

4.1 | Implementation

While there are many ways students can implement AR and SR strategies, one practical method we recommend involves a VR reinforcement based on students' daily flashcard completion. This method uses a pre-existing program named Anki, a free open-source software that uses AR/SR algorithms to improve retention of information through flashcards. (30) Many developers have created public add-ons for users to increase productivity and enhance program features. We chose to utilize Anki as our primary program, instead of other applications, as its resources are easily accessible online and free of charge. In light of this initiative, we have developed an add-on that keeps track of the daily number of cards completed by students.

The decks may be pre-made by senior students or faculty members. However, the faculty will be responsible for standardizing decks to ensure high quality and fair assessment. Medical schools will be able to modify the minimum required number of cards per day. Moreover, the faculty will also be able to modify the amount of content that should be covered per session. For instance, one school may choose to utilize a cumulative format whereas another may prefer shorter, non-cumulative testing strategies. For this reason, decisions will be left up to individual schools to adjust the add-on in accordance with their unique objectives and teaching goals. At the end of each successful day, the add-on will automatically reward students with a grade percentage using a VR reinforcement system. For example, a student may successfully complete their decks for two days and receive a reward on the third day in the amount of 0.5%. Meanwhile, another student will receive their reward on the fourth successful day. This will motivate students to continue using the decks on a daily basis as they do not know when the reward will be given. The addition of all rewards will maximally equate to 10% by the end of the semester (or the agreed-upon percentage by the faculty). The mark will then be incorporated into the traditional semester marking scheme to incentivize daily completion of cue cards. Depending on the medical school, the way students acquire cards may differ. Some schools may choose to provide students with faculty-reviewed cards, student-curated decks, or United States Medical Licensing Exam (USMLE) decks found online free of charge. Alongside establishing a question bank, there also needs to be time dedicated to educating students about this initiative and incorporating it into the traditional marking scheme. Medical schools will need to adequately educate students on the benefits of such initiative and provide them with training for the designated software.

In addition to utilizing evidence-based learning strategies and an incentivized participation system, this method provides some additional benefits. First, by incorporating an evidence-based approach to learning and reward, medical schools could potentially assist students in coping with new academic challenges. This would be achieved by shifting the yearly marking scheme from a traditional examination approach to a more engaging daily incentive building initiative. Research has shown that, among other factors, participation and high self-efficacy beliefs among medical students contributed to higher test performances and increased motivation for learning. (31) As such, participation in the proposed activity will allow students to be constant participators and will provide rewards. This will increase self-efficacy and motivation, leading to better overall performance. Furthermore, given the data collected by the software, it will be possible to track the progress of students and to acknowledge the material that students find difficult. Faculty can then use this knowledge when updating or designing exams or other assessments. Moreover, faculty can determine large areas of content that are difficult for students to grasp and dedicate more time and resources to teaching this in future years. The discussed method should not consume much of the staff's limited time as it will only require the initial setup of the question bank, which can be re-used each year. The questions may be modified over the years as the medical school curriculum advances and adapts. However, the bulk of the curriculum should remain relatively unchanged as it represents well-established scientific principles.

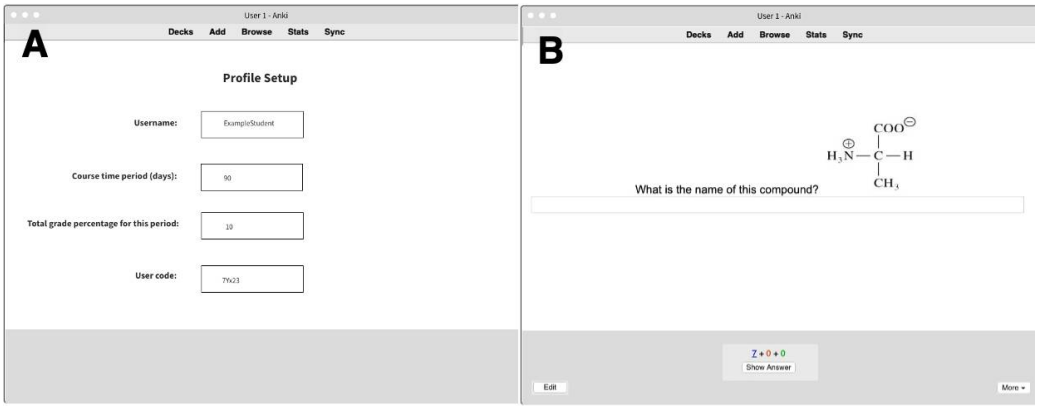

FIGURE 1 (A) Profile setup with customizable variables; (B) Flash card question screen.

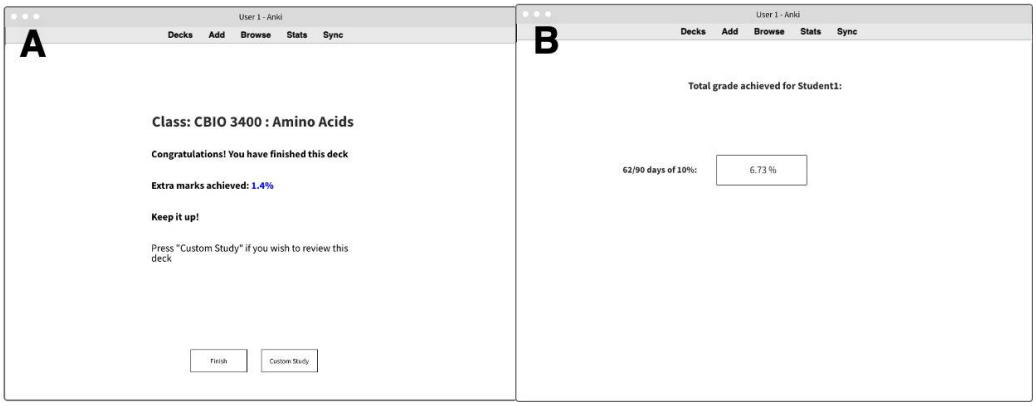

FIGURE 2 (A) Grade percentage given for flashcard session review (end of day); (B) Total grade output screen for given course period.

5 | LIMITATIONS

Despite the presented effectiveness of AR/SR learning strategies, certain limitations pertaining to our initiative need to be addressed. First, since this activity will be done outside the classroom, students may be inclined to simply guess or randomly select answers to obtain participation marks. However, by doing so, students will not benefit from AR/SR and would be misusing their time. It is important to note that AR/SR are effective learning strategies because they are personalized to the individual's knowledge. (24) It is therefore necessary to initially educate students on the efficacy of such evidence-based approaches to incentivize participation. Additionally, the purpose of this study technique is not limited to assessing current knowledge, but rather to encourage students to actively participate and become engaged in the subject material. This rationale is supported by the fact that benefits from AR/SR occur even when responses are not correct. (24) Moreover, the implementation of electronic flashcards may not be suitable for all students, particularly auditory learners. While this initiative may work best for specific groups of students, we believe the concept of utilizing AR and SR should be promoted, even if it is through other means. In the future, we hope to be able to incorporate more Anki add-ons that incorporate different learning strategies. By adding options such as auditory cards or incorporating videos into the explanation of answers, we diversify this learning strategy to more types of learners and facilitate a more inclusive environment. The AR/VR strategy also has the potential to motivate more stu-

dents to begin and commit to these learning strategies. Although the AR/SR/VR initiative could increase student workload, we recommend that routine feedback surveys be implemented to allow faculty to meet the needs of their cohorts and adjust accordingly. As this is paper simply recommends a technique that has not yet been tested in medical education, there are quite a few unknowns. Future studies are needed to comprehend the usefulness of this proposed intervention. Feedback forms are one method that may be utilized to evaluate the student interest and participation in this program. However, experimental studies should be considered to discern true effectiveness by looking at variables including but not limited to: Mental health and well-being of medical students (through self-reported feelings of anxiety, depression, imposter syndrome etc.), scores on exams focused on knowledge acquisition (specifically in the pre-clerkship years), and clinical application skills in clerkship years.

6 | CONCLUSION

Medical education involves a substantial amount of content that must be comprehended and applied successfully before a student can proceed to the next phase of their training. In this paper, we proposed an evidence-based learning approach in which students are motivated to continuously recall content through AR and SR methods. By providing VR incentives in the form of participation grades, students are encouraged to participate in these strategies, which have been proven to increase the persistence of students and minimize extinction. (27) Successful implementation of new strategies will require collaboration among medical school faculty and students. We, therefore, recommend that medical educators implement this strategy and tailor it to their specific curriculum and mission statements.

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A Reflection on the Role of Anatomists in Modern Medical Education: Confronting Meaning and Mortality in the Gross Anatomy Laboratory

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ABSTRACT

Modes of anatomical instruction, especially the need for trainees to dissect cadavers, have been contested for generations. The present reflection provides an opportunity to re-approach this age-old debate and contemplate the state of anatomical sciences education through a narrative reflection of a teaching assistant's encounter with a donor in the cadaveric anatomy laboratory.

KEYWORDS
Cadaveric Anatomy, Gross Anatomy, Anatomical Sciences Education, Medical Education, Medical Student

My right wrist aches as I make the final touches to my chalk sketch of the abdominal wall. Swiveling in place, I see six first-year medical students filing quietly around my designated table. Their eyes are fixed far beyond my station, staring at the collection of concealed bodies arranged symmetrically on either side of the room. I cough gently, with purpose, and hazard a smile, but am immediately met with expressions of veiled apprehension. "It's okay", I tell myself; "This is their first day".

The laboratory feels poorly ventilated, almost cold. My students are staring absently at our donor while I scan the first objective on my lesson plan: "Using proper anatomical terminology, palpate the common surface landmarks on your cadaver". Realizing that our donor is still contained within her body bag, I decide to set down my list of objectives for the time being and take my group to the demonstration body – a donor that has been meticulously pre-dissected by the anatomy in-

structors, allowing students to appreciate the relevant anatomy before tackling any intricate dissections themselves. As I unzip the body bag of this semester's demonstration body and peel back the skin overlying the abdominal wall, revealing our region of interest, I immediately hesitate because the arrangement of the skeletal muscle is so 'textbook', it feels uncanny.

Smiling politely at the eager yet tentative faces gathering around the dissection table, I carefully make my way towards the laboratory manager's office, leaving my students to inspect the relevant gross specimens surrounding the dissection table. "Do we have a cause of death for the demonstration body this semester? I'd like to know before I take my students through the abdominal wall musculature in case there are any relevant pathological abnormalities to review". Given the young age of the donor, I'm expecting to hear cardiomyopathy, brain aneurysm or perhaps glioblastoma. "Of course, just one moment", she replies faintly. "He took his own life after years of battling chronic pain".

Although I had encountered my fair share of death and suffering outside of the anatomy laboratory, something was different. To say that I understood the bewilderment of that moment would be callous and untrue, but perhaps the visceral response was to be expected. Death had to me been typically encountered within the confines of an acute, predictable event, wherein one can seek immediate support from friends and family. In these instances, we orient ourselves to tolerable levels of novelty using a set of pattern recognition mechanisms that scaffold what we know, onto what we do not. Therefore, we subconsciously deduct and reduce complexity, altering our own reality in favour of finding tranquility. Finding myself stuck in this incongruous laboratory environment without any support or prior frame of reference, I had no idea how to reconcile the tragedy of the moment with the need to instruct my students in a calculated manner. The sudden juxtaposition of the affective nature of an academic discipline that relies on the precise scrutiny of human flesh, with the need to remain assertive and reassuring as an instructor, was jarring. It was only in this very moment, after years of precise dissection and meticulous anatomical study, that I realized I was not trained for this.

My gut reaction when confronted with such an existential pressure was to test the strength of our collective resolve. I felt that to share in the tragedy and strange beauty of the moment would create a learning opportunity like no other. These students would have to deal with the stark reality of death almost every day as clinicians, would they not? Surely confessing this truth was not beyond the bounds of the difficulties one might expect to face when entering the cadaveric anatomy laboratory. But on the other hand, who was I to guide these students through a transition that may very well define their budding medical careers? A knowledgeable anatomist, armed with hundreds of clinical cases and targeted dissection techniques, is left largely adrift and unmoored when confronted with the most blatant of human truths. And so, with the weight of the moment slowly suffocating me to the point of compelled action, I quietly explained to my students how our donor came to arrive in the laboratory.

The immense sense of privilege I felt in that moment will stay with me for the rest of my life, and I hope so, too, with my students. The selfless act of body donation establishes a seldom stated yet fundamentally important contract between those who once were, and those who are yet to be. When presented with an inexperienced and faceless explorer, the donor (patient) demonstrates complete trust, even in their most vulnerable state. The young medical student is gifted the opportunity to freely explore the body of a voiceless companion far before they are an accredited healthcare professional. And it is here, in a student's moment of fear and unease, that their instructor may, and perhaps should, choose to imbue a sense of humanity to an otherwise rigid empirical science, denoting the importance of a ritual in medicine which transcends boundaries of life and death.

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An anatomist spends thousands of hours dissecting diverse donors and engaging in a variety of specialized coursework to develop the competency needed to teach (1). It is paramount for the medical student that

their instructor can field questions concerning intricate structural relationships or curious pathological abnormalities. And yet, these same instructors typically spend limited to no hours preparing to teach their students about death and the difficulties of learning in a cadaveric anatomy laboratory (2). Modernization of education in the anatomical sciences has provided an enormous number of learning resources from virtual reality laboratories to 3D phone applications (3,4). Complex anatomy can now theoretically (and soon, I dare say, in practice) be mastered from the convenience of one's living room. In this context, the need for formally trained anatomists in medical education may be dwindling.

Reflecting on this age-old pedagogical dichotomy, where anatomy can be conceptualized as both an immutable science and an iterative study of what it means to be human, we must ask ourselves: is it a disservice to the donor (patient) if this unique environment is not explicitly utilized to help the budding physician develop a sense of moral responsibility? And further, does the anatomist have the training necessary to mediate this nascent patient-physician relationship? Unless we bolster a curriculum that attempts to grasp the ineffable, human side of anatomy, it may be the case that formal cadaveric dissection courses continue to disappear across the country (5). An inter-disciplinary approach to teaching anatomy that is inclusive of disciplines outside of the traditional medical sciences (such as philosophy, anthropology, or sociology) may be a key component in modern medical curricula that strive to maintain gross anatomy laboratories and necessitate the training of anatomists for future generations.

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Addendum: This article was written based on an academic experience that did not occur at McGill University. The descriptions provided in this piece do not reflect the current protocols or opinions of McGill University, its faculties, or departments. Please see our Policy on Published Editorial Materials for more information.

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REFLECTIONS
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Knowledge-Sharing to Enhance Global Health Equity

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ABSTRACT

Knowledge produced by specialized professionals can be shared to promote public understanding and decision-making. During the COVID-19 pandemic, the application, translation, and dissemination of specialized knowledge has informed global policy responses and contributed to new vaccine technologies that protect against disease. However, the pandemic has also highlighted the potential impacts that ineffective knowledge dissemination and misinformation can have on health outcomes, which can further deepen health inequities between groups. Preliminary considerations are suggested for ways to foster a culture of knowledge sharing aimed at promoting global health equity.

KEYWORDS
Knowledge Exchange, Health Equity, Knowledge Sharing

The sharing of specialized knowledge can improve the public's awareness or understanding of technical concepts, processes, or evidence and is often generated by specialized disciplines or professionals. The process, which may be termed as knowledge translation, can be defined as a "dynamic and iterative process that includes synthesis, dissemination, exchange, and ethically-sound application of knowledge." (1) Invariably, the accumulation of this knowledge by key stakeholders and subsequent transfer of knowledge to the general public is a process that will take time. However, in the process of achieving a certain level of expertise, the way that knowledge acquisition by individuals and particular groups can create and deepen pre-existing disparities between us at a fundamental level is a concern that is often overlooked. When parties lack

pertinent information required to carry out critical decisions or when individuals convey information inaccurately, there are concerns regarding how this information, or lack thereof, will fundamentally impact the how stakeholders use such information to guide critical decisions and actions, particularly when these issues are time-sensitive matters. In striving for a society that emphasizes fairness and collaboration, then we must consider how to reduce these barriers through knowledge sharing.

Specialized knowledge can have considerable benefits for society when shared in formats that enable widespread comprehension and active usage. During the past two years of the pandemic, scientific expertise enabled the creation of COVID-19 vaccines that have been estimated to avert thousands of deaths. (2) Specialized expertise has also contributed new insight on the biological and sociocultural impacts of the virus that has helped formulate policy responses and adapt services across a range of industries. In the brink of the current pandemic, to fight the common enemy of COVID-19, it is the practice of knowledge-sharing and communication across borders that led nation-states to devise a global strategy to "flatten the curve." (3)

But when this knowledge is not communicated well, delayed, or ignored in the time of a global crisis, the international response to the current pandemic has its flaws. The pandemic has revealed the dangers of group ignorance and the spread of misinformation that requires concerted, interdisciplinary action. One example that highlights the detrimental effects of miscommunication is the recent development of consumers ingesting drugs not authorized by the Food and Drug Administration (FDA) or Health Canada (HC) (4,5). There has been a rising interest in using Ivermectin, a drug ordinarily used for animals, to treat or prevent COVID-19. Not only is the drug dangerous when taken in large quantities, (6) there is no evidence from clinical trials to support the belief that this drug proves to be effective in fighting the virus. (6) Importantly, the FDA and HC has not approved this medication. (4,5) This is only one example. Over the course of the pandemic, we have seen far more severe examples of the impact of the spread of false and misleading information. Around the globe, there have been countless instances of violence against doctors linked with a reporting of general increase in violence in health care settings including in India (7) and Latin America. (8) Lack of access to accurate information about COVID-19 vaccines, combined with prevailing mistrust against medical professionals, has been linked to vaccine hesitancy and low vaccination rates among certain ethnic groups. (9) Others have highlighted how the lack of data on race, ethnicity, and health conditions in Canada may prevent the generation of evidence needed to adequately understand whether certain groups of people are more prone to disease. (10) In Canada, disparities in health outcomes are further compounded by the lack of health and technological literacy, which remain highly variable across communities in Canada. (11) Worldwide, there is only an estimated 14% who could not read or write as of 2016. (12)

Even when credible and experienced experts create knowledge through research and development and thus involve themselves in the process of knowledge creation and ultimately knowledge-translation, it may be challenging to share with others the information we acquired. Particularly, knowledge sharing may be difficult for those who are not familiar with best practices for communicating complex facts while considering the cultural complexities and nuances that underlie these facts. While doing so may provide a significant benefit, going the extra mile in every case may prove to be costly and mentally taxing. For instance, the implementation of these heightened expectations may be viewed as onerous due to additional demands on time that contribute to increasingly higher rates of burnout at work. (13)

In a wider context, knowledge-sharing raises systemic challenges. Within the academic publishing industry, there are few incentives to establish public communication within the academic community. For instance, the number of peer-reviewed journals that require a plain language summary with submission of a manuscript is fairly limited, although the number is growing. (14) Similarly, some funding agencies, another key player in the academic arena, only require a submission of a "knowledge-sharing plan" for two grants pro-

grams offered by the Canadian Institute for Health Research. (15) Globally, gaps in research training, development and infrastructure remain, particularly for nations already bearing the burden of global infectious diseases. (16) It begs the question then, what is the benefit of highly coded information when only few have ciphers to decrypt them?

One approach to enable us to accomplish equitable access to knowledge-sharing is through a collaborative process. In turn, this may permit us to improve the accurate and efficient use of information. Some emerging models are challenging the way evidence-generation and sharing is done itself, such as participatory research that include knowledge users or living evidence reviews that bridge the evidence-practice gap through real-time updates. While progress towards accessible knowledge-sharing remains to be made, we propose some key considerations based on this precedent as tentative starting points to re-invigorate dialogue on how to engage individuals and organizations who create, hold, and consume knowledge:

1. **Communication training.** Training program curriculums should explore ways to develop communication skills and content delivery in the context of cultural considerations to deliver intended meanings with care and accuracy to different groups. Ideally, these materials should be co-created with people with lived experiences, communication specialists, and those from the creative sector who have implementation experience.
2. **Open-source or access resources.** Journals and funding agencies have a role in easing access to knowledge via support to ensure free access to papers, have transparent reporting requirements in line with established research guidelines, and require end-of-grant dissemination plans.
3. **Development of novel frameworks for data collection and research.** Accelerate and improve the implementation of research by advocating for new approaches to knowledge generation and dissemination itself, such that it is inclusive by design irrespective of disciplinary boundaries.

At the individual level, knowledge-sharing can also be rewarding on its own. In the context of mentoring, sharing and passing of knowledge in a broad spectrum of industries (17-19) is linked to increased awareness of discipline knowledge (20), enhanced career satisfaction (19), and feelings of connectedness to one's peers and self. (17, 18)

From the community perspective, engaging the public in meaningful exchange also provides unique perspectives, which can boost trustworthiness in decision-makers and guide policies. (20) As a health intervention, education and training have shown the potential to lift whole communities out of poverty and provide the momentum needed to make sustained upward trajectories throughout life. (21)

More broadly, knowledge-sharing has the potential to provide other benefits for ourselves and our diverse communities as the transfer of information empowers communities to take action and guides policymakers to make more informed decisions that can lead to improved health outcomes, especially for historically underserved groups such as minority women. Some evidence also suggests that committing resources and other investments to educational attainment for minority women improves maternal health outcomes by increasing their economic opportunities and decision-making power within the home including those related to their own healthcare, which can lead to changes in their fertility practices. (22) These significant benefits further emphasize the critical importance for continued support, funding, and implementation of programs that aim to promote knowledge exchange with the public so that they reflect the perspectives of the very communities in which this knowledge may be disseminated and used.

Because of the global pandemic, many of us have spent the last two years far removed from our loved ones. But we have learned that constructive relationships between communities and other key players, strengthened by the sharing of knowledge and creation of trust, make engagement with our communities not only desirable, but necessary. From these stronger relationships, it is our hope we will seek how knowledge can

unite us and inform decisions that improve the livability and harmony within our communities as we continue to reconsider and reflect on whether our current approach to resolving the global pandemic is effective and importantly, how we can change our course to make access more equitable.

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REFLECTION
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Promoting Self-Care Among Youth with Type 1 Diabetes Mellitus.

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ABSTRACT

Each year, diabetes camps provide fun, stimulating, and safe experiences to approximately 20,000 children across North America. At camp, children and teenagers with diabetes connect with one another in an inclusive and welcoming environment, designed to meet their social, emotional, and medical needs. A multidisciplinary team of allied healthcare professionals are on-site as well to encourage and facilitate campers' acquisition of disease management strategies.

Camp Carowanis is a specialized camp for children with Type 1 diabetes in Sainte-Agathe-des-Monts, Quebec. The camp offers youth a memorable summer experience, where they are empowered to become more autonomous in managing their diabetes. The site also serves as an undergraduate medical education elective in pediatric endocrinology for clerkship students at McGill University.

In this article, Laura Pinkham, a third-year medical student at McGill University, shares her observations on the opportunities for promoting self-care among children with type 1 diabetes at Camp Carowanis.

KEYWORDS
Type 1 diabetes, Camp, Pediatrics, Self-care, Self-management

A REFLECTION ON TYPE 1 DIABETES MANAGEMENT AND SELF-CARE AT CAMP CAROWANIS

'Hey, do you think I could start using an insulin pump?' a curious camper asks, looking up at me with interested eyes as I scan his plate, double-checking the number of carbohydrates before his lunchtime insulin injection. 'Oh, for sure, look how easy it is! Plus, then you don't have to prick yourself with needles all the time' chimes in another enthusiastic camper, manipulating his insulin pump with ease and showing his tent buddy how it works.

As I think about the benefits of insulin pumps versus injections in pediatric patients with type 1 diabetes mellitus (T1DM), the campers have changed subjects and are now chatting about the prize they won during their morning activity. It's my second day on the medical team at Camp Carowanis, a specialized summer camp for children with T1DM. I'm trying to catch up on the knowl-

edge and skills the kids seem to demonstrate rather effortlessly, so I can appropriately manage their glucose levels over the next ten days.

T1DM is one of the most common chronic diseases affecting pediatric patients in Canada. The autoimmune disorder destroys insulin-producing beta cells in the pancreas. (1) Without adequate insulin levels, glucose is unable to enter the body's cells and instead accumulates in the blood. Immediate symptoms of hyperglycemia include thirst, increased urination, fatigue, and blurred vision. (1) More long-term complications include damage to small and large vessels. (2) Exogenous insulin therapy is the mainstay of treatment to manage glucose levels, which are influenced by a variety of factors such as food, activity levels, stress, and insulin. (3-5) At Camp Carowanis, the interprofessional team strives to anticipate and manage these variables to provide campers with a safe and fun experience.

Beyond maintaining glycemic control, an important role for the staff at Camp Carowanis is to promote self-care among campers. Self-care can be broadly understood as behaviors and actions undertaken by individuals to promote their wellbeing. (6) In the context of a chronic illness, self-care also involves health-related activities required for daily living. (7, 8) For children with T1DM, self-care entails monitoring glucose levels, disinfecting injection sites, administering insulin, and preventing and managing hypoglycemic episodes, among others.

Existing literature has established the importance of children with T1DM developing self-care skills to promote long-term health and minimize the risk of disease-related complications by keeping glucose levels within a safe range. (8) Self-care skills also increase children's autonomy and confidence in managing their illness. In turn, medical and nursing students at Camp Carowanis assess campers' comfort levels with different disease management activities and build on their existing skillset.

The discussions surrounding self-care come up naturally at camp, and I'm immediately impressed by the campers' engagement. They ask me why their insulin dose was adjusted at dinner time, if they can change their fixed carbohydrate meal plan to eat more snacks before bed, and how to prevent having another low during water sports. We talk through each decision that intrigues them, and I'm given the opportunity to share the knowledge I've recently acquired. At the same time, campers share hints with me on how to remember long-acting versus short-acting insulin by the needle encasement colors. They let me know how the current insulin doses are working for them, and our team reviews their prescriptions daily. The campers are patient and gracious in a way I couldn't have imagined as I learn about this disease that imbues their daily lives and we explore self-care practices together.

Mealtimes at camp are ideal opportunities to promote best practices in self-care, as medical and nursing trainees visit each tent to verify carbohydrate counts and supervise insulin administration. As I remind a camper to clean her injection site at lunch, she sighs audibly as the rest of her friends have already begun eating and she wants to join them. She proceeds to take an alcohol swab and clean her lower abdomen, showing me the units on her insulin pen before injecting the dose. I take the encased needle from her and make a mental note to see her first at dinner, so she isn't the last one to start her meal again.

Being in a fast-paced and immersive environment like camp is a great setting for trainees to quickly assimilate new knowledge and skills, but the learning curve can be steep. As the days progress, I become more confident in the knowledge and skillset I've acquired, and the campers become more autonomous in a range of different tasks related to their disease management as well.

The degree of self-care undertaken by pediatric patients is affected by their age, maturity, interest levels, and the support network and resources available to them. (9) The number of self-care responsibilities to manage T1DM in pediatric patients can be overwhelming, particularly at the time of diagnosis. (10) For some campers, this is their first year living with diabetes, and members of their support network may assume many of the tasks required to manage their illness. Specific approaches to enhance the adoption of self-care practices among children with diabetes is an area of ongoing research. (9, 11) However, specialized camps for children

with diabetes have demonstrated psychosocial benefits on campers, including an increase in self-care independence. (12)

At Camp Carowanis, children can expand their disease management skillset to include activities like changing their own subcutaneous insulin catheters or updating the settings in their insulin pumps. New practices are taught by medical personnel at the camp's clinic, but are also sprinkled throughout mealtimes, boating rides, and walks between activities. At the camp's session-based award ceremonies, self-care practices are recognized alongside campers' archery and swimming skills.

The award ceremonies are also opportunities to highlight the contributions of adolescent campers participating in Camp Carowanis' unique six-week leadership program. Twelve adolescents are selected annually to participate in the program, designed to meet the needs of teenage campers and promote their development as a leader within their communities. The *Leaders program* includes a provincially recognized camp counsellor certification, specialized training to meet the needs of campers living with diabetes, and medical education sessions which teach participants the fundamentals of insulin dosing.

During their first week at camp, leaders participate in an interactive session with the camp's medical director, pediatric endocrinologist Dr. Preetha Krishnamoorthy, to learn how and why changes are made in the administration of basal and bolus insulin doses. The session mirrors the training provided to medical students, pediatric residents, and pediatric fellows joining the Camp Carowanis team for a rotation.

Following the training session, leaders are given copies of their medical charts to identify trends and patterns in their glycemic control. A collaborative relationship takes form between the leaders and the on-site physician, who may share suggestions via a colorful post-it as needed. Leaders thus take on greater self-care responsibilities than they did as campers, ensuring continuous growth and self-development at Camp Carowanis.

Over the course of a two-week session, campers and leaders make new friends, try novel activities, and hone self-care skills to optimize their diabetes management. Simultaneously, healthcare students acquire the essential knowledge and skills that underpin effective diabetes management in pediatric patients. At the end of a session at Camp Carowanis, campers, leaders, and trainees alike leave with a greater appreciation and understanding of how to live a healthy and fulfilling life with T1DM.

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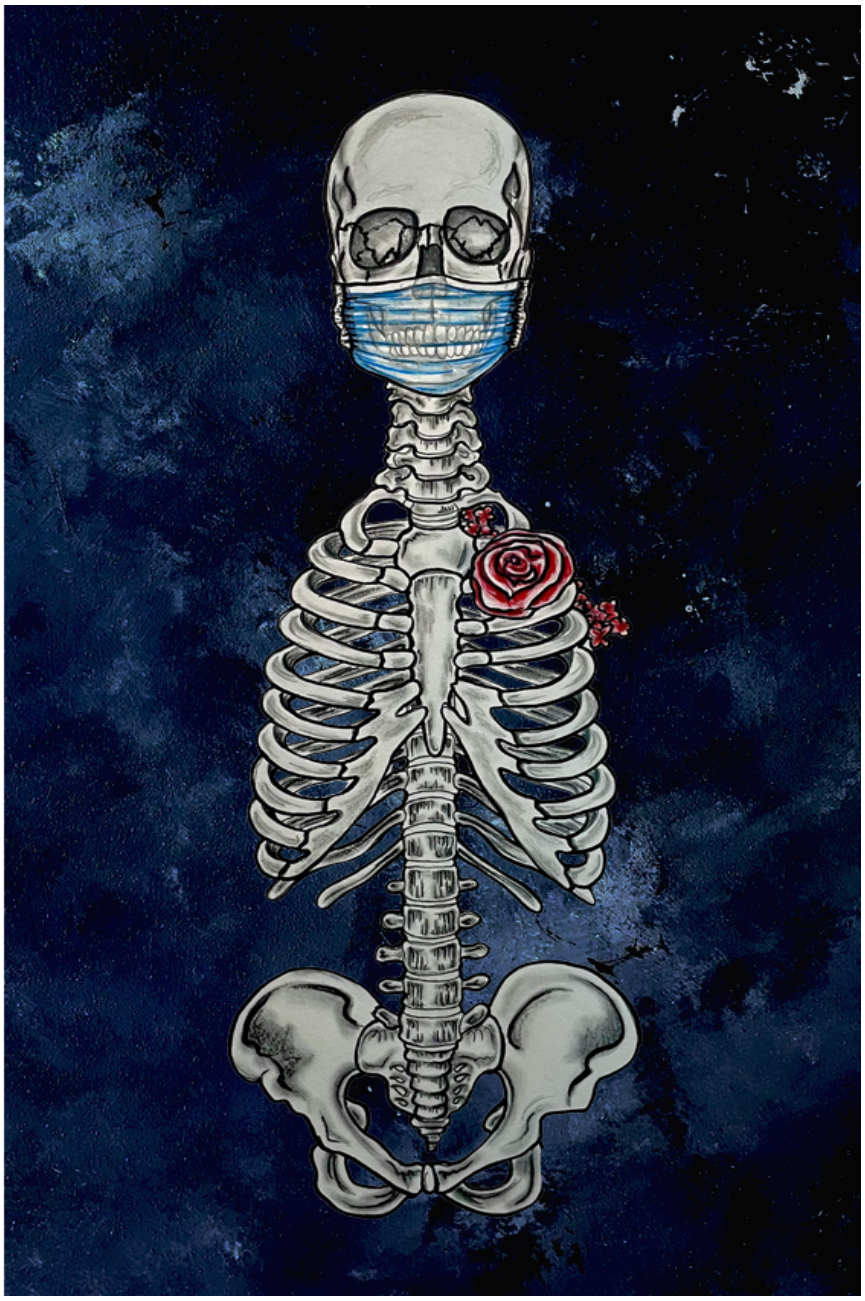
LETTER TO THE EDITOR



Artist: Caroline Najjar

LETTER TO THE EDITOR
McGill Journal of Medicine

The Impact of COVID-19 Pandemic and Associated Restrictions on Skin Cancer Diagnosis and Treatment in the Western World.

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KEYWORDS
Skin Cancer, COVID-19, Cancer diagnosis

The COVID-19 pandemic has had a significant impact on healthcare services worldwide. Outpatient dermatology services have experienced a substantial decline in referrals and consultations. (1-3) Prior to the pandemic, dermatology referrals for skin cancer had been increasing for several years. However, since the start of the COVID-19 pandemic, there has been a decrease in the diagnosis and treatment of skin cancer in Canada and in other western countries. (4) Although the information about the number of dermatology referrals, skin biopsies and skin cancer diagnoses in Canada is limited (4), statistics from the United Kingdom and the United States are available. Early diagnosis plays a critical role in improving overall survival in patients diagnosed with skin cancer. Data obtained from the Cancer Tracking Service at Salford Hospital in the United Kingdom noted

as much as a 50% decrease in urgent skin cancer referrals between March and April 2020, when compared to the previous year; this expected to result in a similar reduction in skin cancer diagnoses. (1,5) The decrease in referrals was also observed for several other types of malignancies such as urological, gynecological and colorectal. (1) The reduction in referrals for suspected skin cancer is of great concern to the general population as it presumably means that more patients will present later on with advanced stages requiring more morbid surgeries and overall worse prognoses. The reduction in dermatology consultations and skin biopsies is likely related to several factors, as described by Ibrahim et al in 2021. (2) Fear and anxiety related to contracting COVID-19 dissuade many patients from presenting for in-person assessments. Patients may avoid using telemedicine if they have a skin lesion located on the genitalia, perineum or breast. Elderly individuals at higher risk of developing skin cancer, may have difficulty navigating virtual systems. (2) Moreover, the need for specialized equipment, reliable high-speed internet connection and computer knowledge may represent significant socioeconomic barriers for certain patients. (2) Additional factors are likely limiting access and effectiveness of teledermatology for various populations; however, more qualitative data is needed to address these elements. There has been a significant increase in telemedicine use among healthcare providers since the start of the COVID-19 pandemic. Although telemedicine has limitations, it can help with the timely diagnosis of skin cancers, when presenting to a clinic for an in-person evaluation is not possible. Dermatologists working in a university setting or a public-sector were 20% more likely to use telemedicine than private practitioners. (3) However, dermatologists that have been in practice for more than thirty years were less likely to use telemedicine. (2) Despite the widespread use of telemedicine, the amount of skin cancer referrals and biopsies have not recovered to quantities seen prior to the pandemic in the United Kingdom or the United States. (1-3, 5) The specific long-term effect of this decline remains unknown at the moment, but an increase in mortality and morbidity due to skin cancers is anticipated. More research is needed to study the effect of COVID-19 on skin cancer outcomes in Canada.

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APPROACH TO

Artist: Jenny Xinyu Ji

APPROACH TO
McGill Journal of Medicine

Pneumonia in Immunocompetent Patients

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ABSTRACT

Pneumonia is a leading cause of morbidity. Pneumonia is defined as a lung inflammation of infectious etiology. It can be subcategorized into Community Acquired Pneumonia, Hospital Acquired Pneumonia and Ventilator Acquired Pneumonia. Validated scores including the CRB-65, CURB-65 and PSI can guide decision-making between inpatient and out-patient management of pneumonia. While mild presentations can be managed through empiric treatment alone, more acute cases require identification of the infectious agent, initiation of empiric therapy, and subsequent de-escalation of treatment to the identified pathogen. This article aims to provide a framework for junior trainees to diagnose and manage pneumonia.

KEYWORDS
Community Acquired Pneumonia, Hospital Acquired Pneumonia, Ventilator Acquired Pneumonia, Empiric Treatment

1 | QUESTION

A 66-year-old male presents to the emergency room with a history of non-productive cough for the past five days. The patient also reports subjective fever for the past five days, and shortness of breath for the past three days. He explains that initially his symptoms were mild and tolerable but have gotten progressively worse since yesterday, prompting him to seek medical attention today. He has known hypertension, for which he takes ramipril. His past medical history is otherwise unremarkable, and he has no recent travel history.

On examination, he is alert and oriented, slightly tachycardic (108 bpm), tachypneic (29 breaths/min), with an O2 saturation of 93% and a slightly elevated blood pressure (129 mmHg / 88 mmHg). He appears fatigued. Auscultation reveals wheezing. Oral temperature is 38.4°C. His chest radiograph shows evidence of a diffuse pulmonary infiltrate.

Assuming the most likely diagnosis, what would you do next?

A. Admit him to the hospital and treat with levofloxacin
B. Obtain sputum gram stain and culture
C. Treat out-patient with azithromycin
D. Treat out-patient with gentamicin
E. Treat out-patient with levofloxacin

2 | ANSWER

C. The patient's symptoms are consistent with community acquired pneumonia (CAP), with the pulmonary infiltrates on chest x-ray further increasing the likelihood of this diagnosis. The patient's CRB-65 score is 1. Given that the point was attributed due to the age criterion, he does not need a hospital admission. For outpatient care of community acquired pneumonia, empiric treatment is often sufficient. Azithromycin is a good broad-spectrum antibiotic that will cover common CAP pathogens such as *Streptococcus pneumoniae*. Gentamicin only covers gram-negative bacteria and is therefore inadequate for CAP treatment. Fluoroquinolones such as levofloxacin are not recommended as first-line therapy for out-patient treatment of community acquired pneumonia. (1)

This article aims to provide an initial approach to pneumonia for junior trainees. The data presented follows guidelines from Quebec (Canada) and may not be applicable to other settings.

3 | INITIAL APPROACH

Pneumonia is defined as a lung inflammation caused by an infection of bacterial, viral or fungal etiology. (1) Host immunity, pathogen virulence and inoculum size interplay to modulate the risk of pneumonia. Routes of infection include micro-aspiration, macro-aspiration and hematogenous spread. (2) The most common symptoms are cough, sputum production, dyspnea, pleuritic chest pain, and deterioration in overall health. Common physical examination findings include tachypnea, tachycardia, fever, low oxygen saturation, dullness on percussion, diminished breath sounds, rales and/or rhonchi. (3)

3.1 | Diagnosis

The most commonly ordered test when investigating pneumonia is the chest radiograph (posteroanterior and lateral views). (4) Radiographic findings suggestive of pneumonia include lobar consolidates, pulmonary infiltrates, and/or cavitations. (4) The presence of cavitations indicates tissue necrosis and the development of lung abscesses. In cases of upper lobe cavitations, clinicians must be cautious to rule out *Mycobacterium tuberculosis*. (5)

While chest radiograph (CXR) is the standard imaging test, it has some limitations including poor image quality. (6) Other diagnostic modalities include chest computerized tomography (CT) and lung ultrasound. (6) Although CT scan is more precise and may identify pneumonias that are not detected on CXR, it is associated with increased costs and exposure to radiation. (6) Lung ultrasound may be useful for bedridden and unstable patients for whom it may be difficult to obtain a CXR. (7)

Sputum cultures are warranted for all hospitalized patients with severe illness. (8) However, they have been shown to be effective in identifying the infectious etiology only about half of the time. (8) Rapid molecular tests such as PCR and LAMP have been shown to be promising techniques that would improve testing turnaround time and sensitivity. (8) Yet, some issues still remain in terms of the diagnostic capacity of these tests, and cost effectiveness studies are needed before they are put to use more widely. (8)

3.2 | Classification

Pneumonia can be subcategorized into three different diagnoses based on the context of acquisition: Community Acquired Pneumonia (CAP), Hospital Acquired Pneumonia (HAP), and Ventilator Acquired Pneumonia (VAP). (9) CAP is defined as the development of pneumonia symptoms outside of a hospital setting, or within the first 48 hours of hospitalization. If symptoms occur past the first 48 hours of hospitalization, the appropriate diagnosis is HAP. The third diagnosis, VAP, is defined by symptom development occurring 48 hours after intubation. (9)

3.3 | Community Acquired Pneumonia

CAP is a leading cause of hospitalization and morbidity. (1, 3) The most commonly isolated agent is *Streptococcus*

pneumoniae. Other pathogens include influenza A virus, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. (3) While respiratory viruses, typical bacteria and atypical bacteria are the most common identified etiologies, the pathogen is unidentifiable in up to 60% of CAP cases. (10) Suspicion of a causative agent should be based on the region, season, and patient risk factors. (11)

While the choice between inpatient and outpatient care is usually made by using clinical judgment, validated scores can help support this decision. (3, 12) Previous research reports that the CRB-65, CURB-65 and PSI scores are comparable in predicting mortality, (12) although some data suggests PSI has a stronger predictive power for 30-day mortality. (4) The CRB-65 does not require invasive testing and is simpler to apply. (4) The CURB-65 may be favorable if bloodwork is being ordered, and/or is easily accessible. (4, 11) Evidence suggests that PSI is more accurate for low-risk patients, although it requires more intricate testing including arterial blood gas. (11, 12) All things considered, the use of CRB-65 is favorable in primary care settings. (3, 4) Patients needing hospital admission can further be triaged between a general ward and an ICU admission, according to the criteria listed in IDSA/ATS guidelines. (1) See Table 1 for complementary information.

3.3.1 | Guidelines for Treatment

Once diagnosis and choice of hospital admission have been made, treatment may be initiated. Examples of first-line therapy for outpatient care include select macrolides, tetracyclines and -lactams. If no improvement is observed after 72 hours of therapy, respiratory fluoroquinolones are suggested as second-line options. (3) Since certain conditions can increase the risk of severe illness, antibiotic choice also depends on the presence of patient risk factors (Table 2).

For inpatient treatment, the recommended approach is based on the severity of the disease, with patients admitted to the ICU and those with risk factors receiving more intensive treatment with multiple drugs. (1, 4) It is recommended to order a sputum gram stain and culture, if possible, prior to initiating empiric therapy for CAP patients with severe presentations. (1) Further information on treatment choice, as well as the complete list of patient risk factors, is compiled in Table 2. See Figure 1 for management flow chart.

3.4 | Hospital Acquired Pneumonia

Admitted patients have an increased exposure to pathogens of the hospital environment. Direct contact with care providers, as well as intubation, tracheostomy, and other respiratory interventions can facilitate the spread of pathogens and increase risks of HAP. The most commonly isolated pathogens include gram-negative bacilli and *Staphylococcus aureus*, and clinicians should maintain a high suspicion for drug-resistant organisms. (13)

3.4.1 | Guidelines for Treatment

The main risk factor for a drug-resistant pathogen infection in HAP patients is antibiotic use in the past 90 days. (14) Clinicians must be cautious of the development of septic shock and need for ventilatory support secondary to pneumonia, as they have been associated with mortality. (13, 14)

In stable patients with HAP, physicians usually opt to order a sputum culture prior to initiating empiric therapy. (14) It is recommended that empiric treatment regimens be based on local or site-specific data regarding HAP-associated pathogens and corresponding antibiograms. All empiric treatment regimens for HAP should ideally cover pathogens such as *S. aureus*, and *P. aeruginosa* or other gram-negative bacilli. Aminoglycoside monotherapy should be avoided due to toxicity and poor lung penetration. (14)

3.5 | Ventilator Acquired Pneumonia

For VAP, important routes of infection include microaspiration and tracheal tube contamination. Bacteria form biofilms inside the tracheal tube and contaminate oropharyngeal secretions. As the tube is introduced into the airways, pathogens reach the lung parenchyma and

replicate. (15) While the main causative agent is Pseudomonas aeruginosa, other common pathogens include *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter*, as well as gram-positive cocci such as *S. aureus*. (13)

3.5.1 | Guidelines for Treatment

Risk factors for a multidrug-resistant pathogen infections in VAP patients include: intravenous antibiotic use in the past 90 days, septic shock at the time of pneumonia onset, acute respiratory distress syndrome, 5 days of hospitalization, and acute renal replacement therapy prior to pneumonia onset. (14)

Similar to HAP, stable VAP patients should have bacterial cultures ordered prior to initiation of empiric treatment. The recommended lab investigation, in this case, is a semiquantitative culture of an endotracheal aspirate (ETA). This test was found to be the most sensitive when compared to other testing options for intubated patients (e.g. quantitative ETA, quantitative bronchoalveolar lavage, etc.). (14)

Empiric treatment regimens should be chosen according to local or site-specific data on VAP-associated pathogens and corresponding antibiograms. Empiric treatment regimens for VAP should cover pathogens such as *S. aureus*, and *P. aeruginosa* or other gram-negative bacilli. It is also recommended that the use of aminoglycosides and colistin be avoided. (14)

4 | BEYOND THE INITIAL APPROACH

4.1 | Considerations for Management

Whenever bacterial cultures are ordered prior to initiation of empiric therapy, treatment should be de-escalated to target the isolated pathogen. (1, 14) Since pneumonia is a presentation that can frequently lead to sepsis, blood cultures should be ordered to investigate bacteremia in severe presentations. (16)

Due to the association of pneumonia and pleural disease, clinicians must also be cautious of the development of effusion and empyema in patients not improving despite treatment. In these conditions, the patient may require invasive interventions including tube thoracostomy. (17)

For CAP, the course of antibiotics should last >5 days as a general rule. (1) For HAP and VAP, the recommended treatment duration is 7 days. (14) In all cases, treatment should only be discontinued once the patient reaches clinical stability. (1, 14)

The following evidence-based measures may be used to evaluate the patient's clinical stability: ability to eat, normal mentation, and vital signs including heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature. (1) Procalcitonin levels may also be useful to determine if antibiotics should be discontinued, especially in patients with HAP or VAP. (14)

4.2 | Epidemic Pathogens

Additional tests may be recommended if the patient is suspected to have been exposed to epidemic pathogens. To identify influenza, a molecular assay test is recommended. In influenza positive patients, it is recommended to treat with oseltamivir or zanamivir. (11) For *Legionella*, a urinary antigen test will be useful. (14) If SARS-CoV2 is suspected, a nucleic acid amplification test (NAAT) should be ordered. (18)

In patients with viral infections, clinicians must remain cautious of the development of bacterial superinfections, as secondary infection with *S. aureus* or *S. pneumoniae* has been linked with significant morbidity. (19)

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5 | TABLES & FIGURES

CRB-65[a]	
Score	**Recommendation**
0	Very low risk; usually does not require hospitalization
1	Consider hospitalization; If 1 point is given due to the age criteria, use clinical judgment
2	Hospitalize
3 or 4	Hospitalize

CURB-65[b]	
Score	**Recommendation**
0	Low risk; consider home treatment
1	
2	Short inpatient hospitalization or closely supervised outpatient treatment
3	Severe pneumonia; hospitalize and consider admitting to intensive care
4 or 5	

CRB-65 and CURB-65 clinical factors (1 points each)
Confusion Blood urea nitrogen >19 mg per dL Respiratory rate ≥30 breaths per minute Systolic blood pressure <90 mm Hg or Diastolic blood pressure ≤60 mm Hg Age ≥65 years

IDSA-ATS 2019[c]
Minor criteria
Respiratory rate ≥30 breaths per minute Pa_{o2}/Fi_{o2} ratio ≤250 Multilobar infiltrates Confusion/disorientation Uremia (blood urea nitrogen level ≥20 mg/dL) Leukopenia due to infection alone (white blood cell count <4,000 cells/μL) Hypothermia (core temperature <36 °C) Hypotension requiring aggressive fluid resuscitation
Major critera
Septic shock with need for vasopressors Respiratory failure requiring mechanical ventilation

PSI	
Score	**Recommendation**
<51	Outpatient therapy should be considered, especially if score ≤70
51-70	
71-90	
91-130	Patient should be hospitalized
>130	

PSI point distribution and risk factors	
Points	**Risk factor**
Age (years): ___	Men
Age (years) - 10: ___	Women
+10	Nursing home resident
+30	Neoplasm
+20	Liver disease
+10	Heart failure
+10	Stroke
+10	Renal failure
+20	Altered mental status
+20	Respiratory rate ≥30 breaths per minute
+20	Systolic blood pressure <90 mm Hg
+15	Temperature <35°C or ≥40 °C
+10	Pulse rate ≥125 beats per minute
+30	Arterial pH <7.35
+20	Blood urea nitrogen >30 mg per dL
+20	Sodium <130 mmol per L
+10	Glucose ≥250 mg per dL
+10	Hematocrit <30%
+10	Partial pressure of arterial oxygen <60 mm Hg
+10	Pleural effusion

TABLE 1 CRB-65, CURB-65, PSI and IDSA-ATS summary

[a]CRB-65 - Confusion, Respiratory rate, Blood pressure, 65 years of age and older.

[b]CURB-65 - Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older.

[c]IDSA-ATS 2019 guidelines - Patients should be considered for ICU admission if they satisfy either 1 major criteria, or 3 minor criteria.

Adapted from:

Institut national d'excellence en santé et en services sociaux. Pneumonie acquise en communauté chez l'adulte [Internet]. 2017. Available from: https://www.inesss.qc.ca/fileadmin/doc/CDM/UsageOptimal/Guides-serieI/INESSS_Annexes_Rapport_GUO_PAC.pdf.

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COMMUNITY-ACQUIRED PNEUMONIA			Antibiotic combinations		
OUTPATIENT TREATMENT	**First-line**	**Second-line**	**A**	Macrolide (Clarithromycin or Azithromycin), Tetracycline (Doxycycline), Beta-lactam (High-Dose Amoxicillin)	
Risk Factors[a]: Absent	Choose one from **A**	Choose a different one from **A** **OR** Dual-therapy (one from each list) from **B**	**B**	High-dose amoxicillin, Amoxicillin-clavulanate	Clarithromycin, Azithromycin, Doxycycline
Risk Factors[a]: Present	Dual-therapy (one from each list) from **B**	Choose one from C	**C**	Levofloxacin, Moxifloxacin	
INPATIENT TREATMENT	**General ward admission**	**ICU admission**	**D**	Ampicillin-Sulbactam, Cefotaxime, Ceftriaxone OR Ceftaroline	
Baseline coverage (Risk Factors[b]: Absent)	Choose one each from **D & E** **OR** one from **C**	Choose one from **D** **AND** one from either C or **E**	**E**	Clarithromycin, Azithromycin	
Risk Factors[b]: Present for MRSA	Baseline coverage above + Choose one from **F**		**F**	Vancomycin, Linezolid	
Risk Factors[b]: Present for *P. Aeruginosa*	Baseline coverage above + Choose two from **G**		**G**	Piperacillin-Tazobactam, Cefepime, Ceftazidime, Imipenem, Meropenem, Aztreonam	

TABLE 2 Antibiotic therapy for community acquired pneumonia, according to inpatient or outpatient care and presence of risk factors.

[a]Outpatient: Risk factors to consider include smoking; antibiotic use in the past 90 days; chronic heart, lung, kidney, or liver disease; diabetes mellitus; alcohol dependence; immunosuppression.

[b]Inpatient: Specific risk factors for MRSA or P. Aeruginosa include: Previous infection with the pathogen, recent hospitalization, recent use of parenteral antibiotics, site-specific risk factors for either pathogen.

Adapted from:

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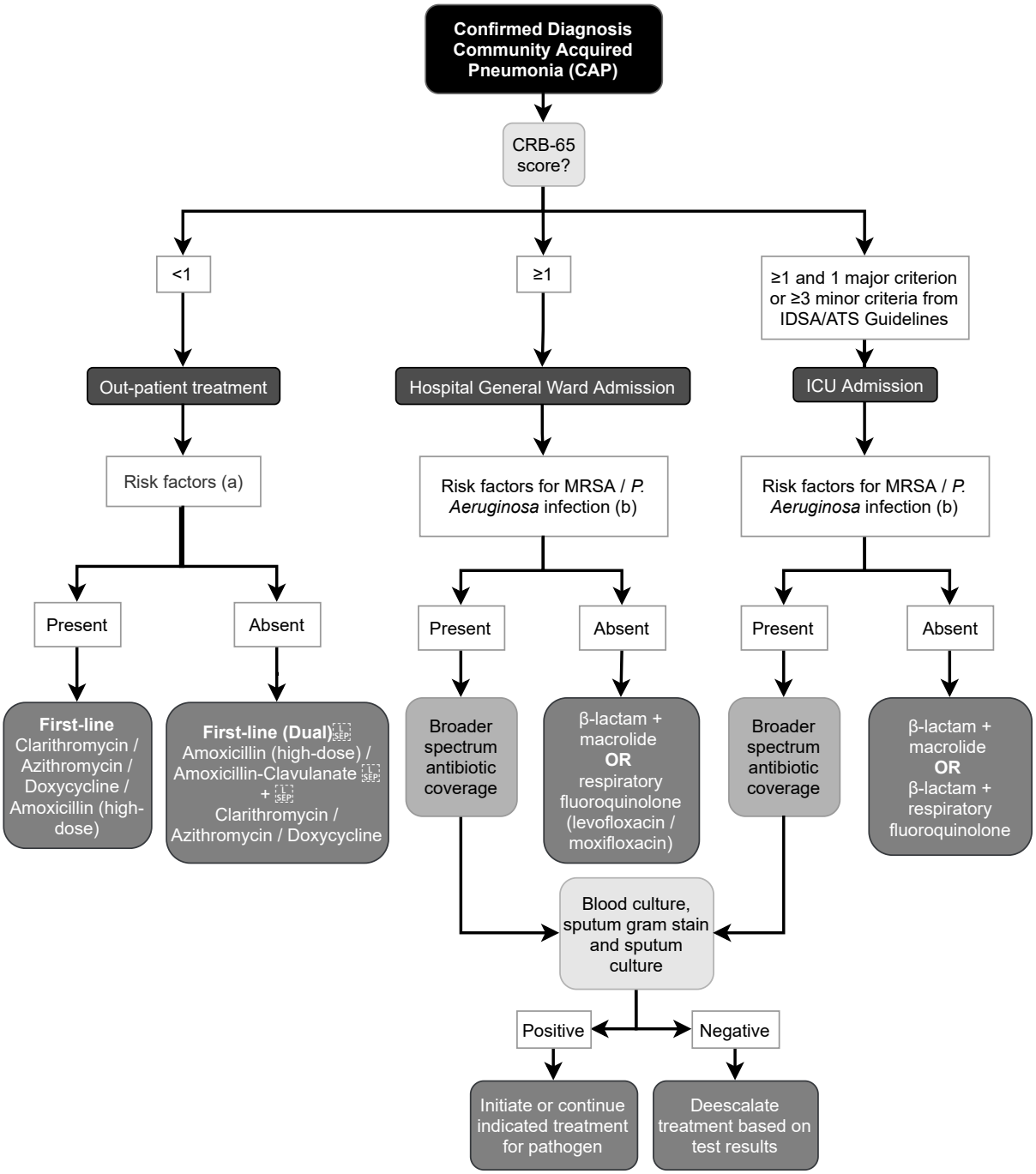

FLOWCHART 1 Flow chart for management of community acquired pneumonia

[a]Outpatient: Risk factors to consider include smoking; antibiotic use in the past 90 days; chronic heart, lung, kidney, or liver disease; diabetes mellitus; alcohol dependence; immunosuppression.

[b]Inpatient: Specific risk factors for MRSA or *P. aeruginosa* include (10):

· Previous infection with the pathogen

· Recent hospitalization

· Recent use of parenteral antibiotics

· Site-specific risk factors for either pathogen

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APPROACH TO
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Management of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a condition that affects up to 50% of men over the age of 50; the condition's prevalence increases with age, particularly after the age of 40. (1, 2) BPH can lead to lower urinary tract symptoms (LUTS) which can have a significant negative impact on health-related quality of life (HRQoL). (2-4) Men presenting with a gradual onset of LUTS are often suspected to have BPH. However, the clinician must recognize that LUTS possess many different aetiologies. This article aims to provide medical students with a stepwise approach to the diagnosis and management of LUTS that are secondary to BPH. The outlined approach describes the differential diagnoses, required investigations, and management-related details for LUTS that are secondary to BPH. This approach is based off of relevant Canadian, American, and European urological association guidelines.

KEYWORDS
BPH, LUTS

1 | QUESTION

A 54-year-old male presents to your clinic with a concern about his urinary symptoms. He reports having to wake up 2 to 3 times per night to urinate, having a very weak stream of urine, and often feeling incompletely voided after urination. The patient has a family history of prostate cancer. He denies taking any medication or using any recreational drugs. The patient's past medical history is notable for alcoholic hepatitis and hypertension; both are well controlled.

At this current stage, which of the following investigations would you **not** consider?

A. *A formal symptom inventory*
B. *Prostate biopsy*
C. *Serum prostate specific antigen (PSA)*
D. *Urinalysis*
E. *Digital rectal exam (DRE)*

2 | ANSWER

A. A formal symptom inventory such as the International Prostate Symptom Score is recommended at initial presentation. This score allows physicians to objectively assess and keep track of the patient's symptom severity when proposing treatment options. (5)
B. **Although a family history of prostate cancer increases a patient's risk for prostate cancer, he is not known to have a palpable mass or elevated PSA levels. Therefore, a prostate biopsy does not need to be performed at this moment. (5, 6)**
C. Serum PSA is a low-cost and non-invasive test that can be used as a surrogate for prostate size. PSA can be helpful for the detection of prostate cancer, and the test can be offered to all males beginning at age 50 (or beginning at age 40 for patients with risk factors of prostate cancer) with at least 10 years of life expectancy. Therefore, given the patient's age and his family history of prostate cancer, ordering a PSA test would be helpful given proper counselling and the employment of shared decision making. (5)
D. Performing a urinalysis can help in ruling out urinary tract infections, hematuria, urothelial carcinomas, and bladder or kidney stones. All of these disorders should be included in the patient's differential diagnosis. (5)
E. Given that the patient's presentation is suggestive of urinary obstruction, a DRE would be helpful to assess prostate size and to rule out the presence of nodular irregularities (suggestive of cancer) or tenderness (suggestive of infection/inflammation). (5)

3 | INITIAL APPROACH

Patients presenting with a gradual onset of lower urinary tract symptoms (LUTS) are often suspected to have benign prostatic hyperplasia (BPH). However, the clinician must recognize that LUTS can be caused by many different conditions.

3.1 | Patient History and Physical Examination

In order to rule out the most concerning aetiologies when diagnosing BPH, the proposed approach recommends beginning with a thorough history and complete physical examination. (5, 9, 10) The history should provide a detailed description of onset, duration, and severity for the patient's LUTS. The medication history is especially important in the diagnosis of LUTS because many medications, such as antidepressants, diuretics, bronchodilators, and antihistamines, are associated with LUTS. (11)

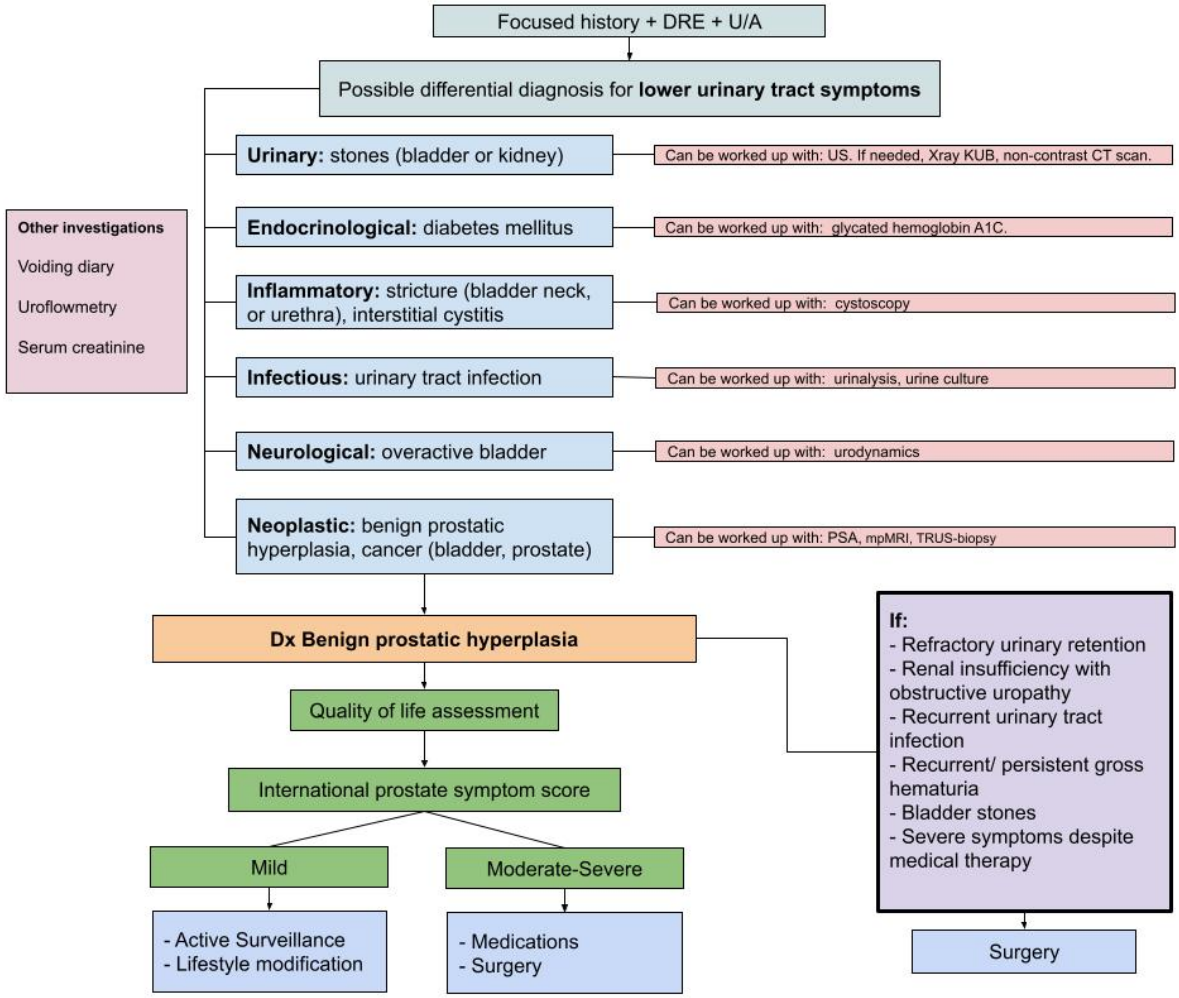
Additionally, if suspected, the clinician must investigate for a history of:

- **Urethral trauma** - suggestive of urethral stricture
- **Gross hematuria** - suggestive of bladder stones, BPH, or cancer
- **Underlying neurologic diseases** - suggestive of neurogenic overactive bladder
- **Diabetes mellitus**
- **Cigarette smoking** - an important risk factor for bladder cancer

The physical exam should include a digital rectal examination (DRE) and an assessment for bladder distention and neurologic impairment. (9, 10) The DRE can be helpful for two reasons: it is an initial screening method for prostate cancer (PCa) and it can serve to roughly estimate prostate volume. (9) Once DRE is complete, the differential diagnoses described in the Flowchart 1 should be further explored, depending on the physician's clinical suspicion, in order to rule out other causes of LUTS.

3.2 | Differential Diagnosis

In the case of LUTS, one of the most important conditions on our differential diagnosis is PCa. Patients are usually screened for PCa after careful counselling with their urologist because most cases of PCa (67%) are considered to be clinically insignificant and do not



FLOWCHART 1 Approach to Lower Urinary Tract Symptoms that are Secondary to Benign Prostatic Hyperplasia.

Treatment algorithm for the diagnosis and management of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). The diagnosis of BPH can be made with a focused history, DRE, and urinalysis in the absence of signs/symptoms of other causes of lower urinary tract symptoms. Further investigations for other possible causes of LUTS are briefly mentioned. The management of BPH relies on the patient's LUTS severity and the impact that they have on the patient's quality of life. Importantly, the recommended investigations included in this proposed approach are usually ordered concomitantly rather than in a step-wise fashion.

Recreated from Badalato et al. (2020). (7)

have an impact on a patient's morbidity and mortality. (12) Pathologically, PCa may present as a mass in the peripheral zone of the prostate and can be easily felt during a DRE. Therefore, if a mass is felt upon palpation it can be indicative of PCa. Due to their peripheral localization, these masses are often not associated with urinary symptoms. However, if a large, localized tumor is present, it can compress the urethra and consequently lead to LUTS. Despite the fact that most patients diagnosed with PCa will experience clinically insignificant disease, it is important to rule out PCa, as it can be life-threatening in specific cases. Importantly, the specificity of DRE is not absolute; patients diagnosed with PCa may present with no positive findings upon DRE.

If the patient does not have a family history of PCa, and the DRE does not reveal any prostatic masses, PCa

cannot be ruled out in patients presenting with LUTS. The next recommended investigation would be to request a serum prostate specific antigen (PSA) analysis (5, 9, 10, 13). Although some controversy exists, the Canadian Urological Association recommends measuring the PSA level in patients presenting with LUTS that would benefit from treatment of PCa if the former were to be detected with further investigation (i.e. patients with greater than 10 years of life expectancy). Nguyen et al. recommend that PSA testing be carried out through a shared decision-making process because the perceived benefits and harms of PCa treatments may vary within the patient population. (14) As implied by its name, the PSA is prostate specific and not PCa specific. In fact, numerous conditions can lead to an elevated PSA such as: BPH, prostatitis, recent ejaculation, recent DRE, recent urethral instrumentation, and PCa. (5) If both a DRE and PSA yield results suggestive of PCa, the patient should be further worked up for PCa with the help of magnetic resonance imaging (MRI) and guided prostate biopsy. (15)

In the cases where PCa is ruled out, a urinary tract infection (UTI) should be ruled out because it is a more common cause of LUTS. To rule out a UTI, urinalysis can be performed. (9, 10, 13) According to Alawamlh et al. urinalysis is strongly suggested to help rule out hematuria, pyuria, and bacteriuria which are all relevant aetiologies of LUTS. (16) The clinician must remember that in practice these investigations can be ordered concomitantly rather than in a step-wise fashion. Therefore, PCa may not be ruled out by the time the patient is sent for UTI investigations.

Additional and less invasive investigations can be ordered initially, and these include a voiding diary, serum creatinine, and uroflowmetry. If the aforementioned examinations did not help identify the cause of LUTS, the following investigations can be performed for patients with concomitant diseases and/or uncertain diagnoses: measuring post-void residual volume, urodynamics, radiological evaluation of the urinary tract, and a sexual function questionnaire. (5) The latter investigations listed can help rule out causes of LUTS such as overactive bladder (OAB), urethral stricture, and bladder/kidney stones. (9, 10)

3.3 | Symptom Score Assessment

At this stage of the proposed approach, the patient's LUTS are likely assumed to be secondary to BPH. Once a diagnosis of BPH has been confirmed, the patient's LUTS must be reassessed and quantified with the help of the IPSS. (5) The IPSS is a validated questionnaire that quantifies the severity of patients' LUTS such that physicians can treat their symptoms accordingly. (17)

In addition to the seven questions of the IPSS survey, physicians often inquire as to the patient's degree of bother related to their LUTS. This assessment is done with the help of the IPSS-QoL which consists of an additional question that asks patients to rate how they would feel if they were to spend the rest of their life with their LUTS. The score ranges from 0 (delighted) to 6 (terrible quality of life). This question can further assist physicians in determining the appropriate intervention for the patient, using a patient-centred approach. This facet is important because the treatment of BPH is aimed at symptom management and is guided by symptom severity, their degree of bother, and patient preferences. (5) A detailed presentation and description of the IPSS and the IPSS-QoL can be found in Table 1.

Following the completion of the IPSS, patients will be categorized according to their symptom severity in the following groups:

1. **Mild symptoms**: scores of 0-7
2. **Moderate symptoms**: scores of 8-19
3. **Severe symptoms**: scores of 19-35

3.4 | Management

Given its benign nature, BPH does not require immediate treatment in the absence of clear indications, such as refractory urinary retention or renal insufficiency caused by obstructive uropathy. However, if left untreated, BPH can lead to acute urinary retention which can increase the risk of UTIs, bladder stones, and renal damage. (9)

Over the past month	Not at all	Less than 1/5 times	Less than half the time	About half the time	More than half the time	Almost always
1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. How often have you had to urinate again in less than two hours after you finished urinating?	0	1	2	3	4	5
3. How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. How often have you had a weak urinary stream?	0	1	2	3	4	5
6. How often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you get up in the morning?	0	1	2	3	4	5

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
if you were to spend the rest of your life with your prostate symptoms just as they are now, how would you feel about that	0	1	2	3	4	5	6

TABLE 1 International Prostate Symptom Score and Quality of Life Score

The International Prostate Symptom Score (IPSS) or American Urological Association Symptom Index is a validated symptom questionnaire used to assess symptom severity in patients affected by LUTS (8). An additional question related to quality of life is usually added to the IPSS to help evaluate the degree to which a patient is bothered by LUTS.

Retrieved from Barry et al. (8)

Often, patients with mild LUTS will improve over time without treatment. According to society guidelines, it is not recommended that patients with mild LUTS or symptoms that are not bothersome be administered any form of treatment. Instead, patients' symptoms are monitored conservatively with a urologist or primary care physician (watchful waiting), and lifestyle modifications that can help control the severity of a patient's LUTS are implemented. (5, 9) These lifestyle modifications include: avoiding caffeinated beverages, alcohol, and spicy foods; restricting fluids (especially before bedtime); implementing pelvic floor exercises; preventing any form of constipation; and avoiding medication that have effects on LUTS such as diuretics, decongestants, antihistamines, and antidepressants. (5) Medications or surgery are suggested if the symptoms become more bothersome. (5, 9, 18)

Society guidelines recommend that patients with

moderate LUTS be offered pharmacotherapy as part of their treatment. (5) However, if these medications do not help improve LUTS and/or cause undesired side effects, urologists suggest stopping these medications and selecting a new therapy instead. The alternative therapy can be in the form of either a new medical or a surgical approach.

The selection of medications for the management of BPH relies on symptom severity, comorbidities, and side effect profile because all recommended medications have equal clinical effectiveness. (5)

Although all recommended medications for BPH have equal clinical effectiveness, alpha-1-adrenergic antagonists (alpha blockers) are strongly recommended as first-line therapy. (5) Additional medical therapies include phosphodiesterase-5 inhibitors (PDE5I), 5-alpha-reductase inhibitors (5-ARI), or a combination of these two with alpha blockers.

To treat males with severe symptoms, patients can either opt for medical or surgical therapy. Medical therapies are usually prescribed as combination therapies (i.e. alpha-1-adrenergic antagonist + 5-ARIs). Surgery is recommended for patients experiencing LUTS that are secondary to BPH when voiding symptoms are severe, watchful waiting and treatment with medications have been unsuccessful, or if the patient has a preference. (19)

As seen in Flowchart 1, certain clinical presentations call for an alteration to the course of a proposed treatment, regardless of the patient's IPSS score. For instance, if the patient experiences urinary retention, recurrent UTIs, recurrent/persistent gross hematuria, bladder stones, or renal insufficiency, then immediate surgical treatment is indicated. (9)

The number of surgical modalities available to treat LUTS, secondary to BPH, is growing. These options include monopolar transurethral resection of the prostate (TURP), bipolar TURP, greenlight laser photovaporization, enucleation, Rezum, Urolift, Aquablation, open simple prostatectomy, and robotic simple prostatectomy. Before proceeding with surgery, the prostatic volume must be accurately measured with either a transrectal or transabdominal ultrasound, as the availability of these treatments relies heavily on the patient's prostatic volume. (5)

The available surgical modalities for BPH vary in degree of invasiveness, risk of complications, functional outcomes, effects on patient's health-related quality of life, and cost. (3, 20) The variation within these treatments allow patients to select an option that best meets their personal preferences. For example, novel treatments are available to provide better sexual outcomes in the case of postoperative ejaculatory dysfunction—specifically retrograde ejaculation which is a common complication secondary to most surgical therapies. (21) Therefore, implementing a patient-centered approach that emphasizes shared decision making is essential before recommending a treatment for a patient's LUTS secondary to BPH. (22)

To conclude, BPH is a condition that can lead to LUTS which, in turn, can have a significant negative impact on patients' HRQoL. Importantly, the clinician must recognize that LUTS possess many different aetiologies. Therefore, a methodical stepwise approach like the one described should be carefully followed. Currently, many options are available to manage LUTS either medically or surgically. These treatments present their own risks and benefits. As such, a shared decision-making process should be implemented.

4 | BEYOND THE INITIAL APPROACH

4.1 | Alpha-1-adrenergic antagonists (alpha blockers)

Alpha blockers relax the smooth muscle within the prostatic parenchyma and the bladder neck, thus facilitating urination by decreasing luminal resistance. The main advantage of this medication is relatively rapid symptom relief. The main disadvantages of this medication are hypotension and ejaculatory dysfunction. (23) Examples of common alpha-1-adrenergic antagonists are tamsulosin, alfuzosin, and silodosin. (5)

4.2 | 5-alpha-reductase inhibitors (5-ARI)

If patients experience side-effects such as hypotension but still desire medical therapy, they can be switched to 5-alpha-reductase inhibitors (5-ARI). 5-ARIs block the conversion of testosterone to dihydrotestosterone, which is the main molecular signal for prostatic growth. The main disadvantages of this medication are decreased libido, erectile dysfunction, and ejaculatory dysfunction. (23) Examples of common 5-ARIs include finasteride and dutasteride. (5)

4.3 | Phosphodiesterase-5 inhibitors (PDE5I)

PDE5Is relax the prostatic tissue and the bladder neck making it easier to urinate. This medication is also used to treat erectile dysfunction. (23) So, when patients experience erectile dysfunction and LUTS secondary to BPH, these medications are ideal to treat both issues simultaneously. The main disadvantages of this medication are headaches and stomach aches. (23) Additionally, PDE5I are contraindicated in patients taking organic nitrates in any form, as the combination of both medications can lead to severe hypotension. An example of a commonly used PDE5I is tadalafil. (5)

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APPROACH TO
McGill Journal of Medicine

Gynecological Adnexal Masses

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ABSTRACT

Gynecological pelvic masses are a common occurrence in women of all ages. The differential diagnosis is extensive and includes masses of all anatomical components of the female reproductive tract. This simple and refined approach leads the reader through the process of narrowing said differential. A thorough history and physical examination are essential steps that can hint to the appropriate investigations such as reproductive hormone levels, serum cancer biomarkers and imaging. Emphasis is put on ultrasound findings, helping differentiate not only diagnoses, but also the benign or malignant character of the mass. It also highlights the Risk of Malignancy Index I, commonly used in clinical practice to assess the risk of malignancy of a mass. Beyond the initial approach, some diagnoses and their management are discussed, from the very common functional cyst to the worrisome ovarian neoplasm, and mentioning more peculiar findings like tubo-ovarian abscess and leiomyoma.

KEYWORDS
Pelvic mass, Gynecological mass

1 | QUESTION

A 50-year-old female presents to a gynecology clinic after her family physician palpated a mass on her right ovary during a routine physical examination. The patient began menopause a year ago. For 4 months, she has been experiencing fatigue, decreased appetite and bloating, but believes those symptoms are due to the hormonal changes associated with menopause. She doesn't report significant weight loss or other symptoms such as fever, nausea, vomiting, or bladder or bowel dysfunction. She also doesn't report any abdominal pain, uterine bleeding or abnormal vaginal discharge. She has no history of cancer, and her family history is unknown.

Her past medical and surgical histories are unremarkable aside from mild hypertension. The patient is not known for any gynecological conditions such as other pelvic masses, endometriosis or sexually transmitted infections. Her gynecological history is G3P2A1 with two normal vaginal deliveries and one unexplained first-trimester miscarriage.

The patient doesn't smoke or use any recreational drugs but drinks socially twice a month. She is sexually active with one male partner and uses condoms as protection. She doesn't take any medications and is making lifestyle modifications to control her mild hypertension.

Her physical examination is normal, including the speculum examination of the cervix. During the bimanual pelvic exam, a solid, fixed and irregular mass is palpated on her right ovary. The mass is estimated to measure 4 or 5 centimeters. Rectovaginal exam is not performed. The following investigations are performed:

Blood test

Complete Blood Count (CBC) within normal limits
Serum CA-125: 44 units/mL (normal <35 units/mL)

Transvaginal sonography with Doppler

6 cm irregular mass on right ovary with multiple thickened septa and a large solid component. No ascites. Doppler shows high blood flow (colour score 4). Uterus and left adnexa appear normal.

Risk of Malignancy Index I (RMI)

RMI= 396 (normal <250)

What is the next best step to take for the management of this patient?

A. *MRI*
B. *Refer to gynecological-oncologist.*
C. *Mass tissue biopsy*
D. *Surgical resection*
E. *Regional lymph node biopsy*

,

2 | ANSWER

B. The CBC is normal and shows no sign of infection. The serum cancer antigen 125 (CA-125) is elevated, but the specificity of this tumor marker is 71-93% and other conditions, such as endometriosis, could be responsible for its elevation. Thus, further investigations are necessary to assess the risk of malignancy. The ultrasound findings (irregularity, nodularity and solidity), the patient's menopausal state and positive CA-125 all contribute to the elevated RMI, which is used to predict the potential malignancy of an adnexal mass. Taken together, the provided information raises suspicion for malignancy. In this context, the proper management would be referral to a gynecological-oncologist.

3 | INITIAL APPROACH

The evaluation of a woman with an adnexal mass begins by eliciting a complete history from the patient, including a sexual and gynecological history, accompanied by a physical exam with pelvic exam and speculum. (1, 2) Most women presenting with an adnexal mass are asymptomatic and, consequently, the mass is often an incidental finding. (1) In the cases where symptoms are present, they vary greatly according to the location and size of the mass; the most common symptom being pelvic pain. (1) While history and physical examination are essential and can significantly narrow the differential diagnosis, imaging is almost always necessary for definite diagnosis (Fig. 1). (1, 2)

3.1 | History and Symptoms

The differential diagnosis for an adnexal mass is broad and although ultrasound is the most efficient diagnostic method, a thorough history including an assessment of any pain and bleeding can narrow the differential substantially. (1, 2, 4) Pelvic pain, amenorrhea, and abnormal uterine bleeding are suggestive of an ectopic pregnancy. (1) A patient with an ectopic pregnancy can present with tachycardia, hypotension and hemodynamic instability. (2) Dyspareunia, dysmenorrhea and pelvic or abdominal pain are indicative of endometriosis. (1, 2) Pelvic pain associated with fever, nausea, vomiting and vaginal discharge is suggestive of pelvic inflammatory disease or of a fallopian abscess. (1) Abnormal menses can also hint to different conditions; for example, dysmenorrhea or menorrhagia could be suggestive of uterine leiomyomas, while oligomenorrhea and hirsutism are more indicative of polycystic ovarian syndrome (PCOS). (1) In general, the increasing size of a mass is linked to the apparition of symptoms as adjacent structures are compressed. (2) A significant mass such as a fibroid can cause abdominal distension, nausea, vomiting, and bowel or bladder dysfunction. (1, 2) A malignant mass, as it enlarges, can also exhibit these symptoms in addition with canonically recognized systemic symptoms such as fatigue, fever, weight loss, and

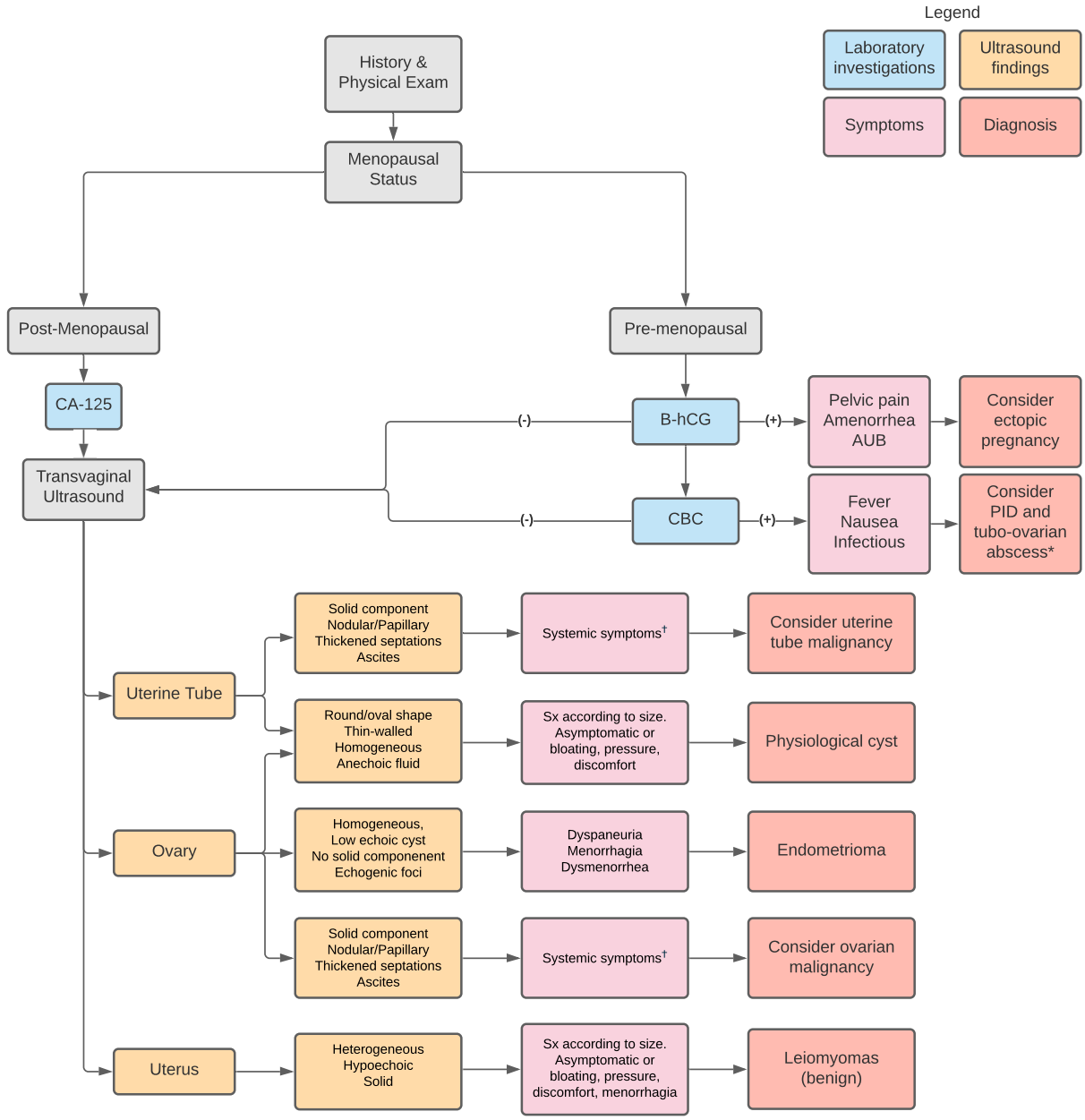

FIGURE 1 Approach to gynecological pelvic masses

This basic algorithm represents the usual management of a patient who presents with a gynecological mass. Including the patient's history and basic laboratory investigations, it is centered on the ultrasound findings which is the modality of choice in the evaluation of a pelvic mass. Common symptoms of specific conditions are indicated but it is crucial to remember that most pelvic masses are asymptomatic.

*Although they are more prevalent in premenopausal women, pelvic inflammatory disease and tubo-ovarian abscesses can also present rarely in post-menopausal women.

†Adnexal malignancies can also be asymptomatic or present with symptoms associated with their size, notably bloating, pressure, discomfort and urinary symtpoms.

AUB: Abnormal uterine bleeding

B-hCG: Beta-human chorionic gonadotropin

CA-125: Cancer antigen 125

CBC: Complete blood count (Note: in this flowchart, it is said to be positive if it shows signs of infection, e.g. elevated white blood cell count)

PID: Pelvic inflammatory disease

Sx: Symptom

night sweats. (1, 2, 3)

3.2 | Blood Tests and Tumor Markers

Blood testing is not always necessary in the setting of an adnexal mass. (1) In general, women of reproductive age should be tested for serum beta-human chorionic gonadotropin (-hCG) in order to rule out pregnancy. (1) In the event pregnancy is confirmed, ectopic pregnancy must be investigated. (1) If the patient presents with fever and signs of infection, a complete blood count is ordered to confirm infection which can point to pelvic inflammatory disease (1) or to a tubo-ovarian abscess. (2) In both of these conditions, WBC count is elevated with a predominance of neutrophils. (2) Tumor markers can raise suspicion for the malignancy of a mass, but they should never be considered as a diagnostic criterion. (1, 3) Cancer antigen 125 (CA-125) is a serum biomarker commonly assessed in post-menopausal women presenting with a symptomatic mass and is associated with epithelial ovarian cancer (OEC). (4, 5) However, specificity is low in early-stage malignancy and in pre-menopausal women; CA-125 can be elevated by multiple physiologic and pathologic conditions such as pregnancy, endometriosis, fibroids and pelvic inflammatory disease. (1, 5) Other tumor markers can be evaluated depending on the patient's age and the characteristics of the mass. In women under the age of 40 years old, tumor markers such as hCG, lactate dehydrogenase, alpha-fetoprotein, and inhibin should be included to assess for rare tumors such as germ cell tumors and sex-cord stromal tumors. (4) Women presenting with bilateral masses or with suspected tumor metastases should be evaluated for tumor markers such as carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 15-3. (4)

3.3 | Transvaginal Sonography (TVS)

Sonography is the imaging modality of choice when it comes to adnexal masses, as it allows the physician to locate and characterize the mass. (1, 2, 3) TVS should be performed in combination with color Doppler ultrasound. (4) Location and characteristics of the mass can be highly suggestive of a diagnosis. Simple cysts, which can be ovarian, paraovarian or paratubal, are non-solid and the transmission of ultrasound signals will not be impaired; therefore, they appear as homogeneous round or oval thin-walled cysts with anechoic fluid in the cavity (Fig. 2A). (6, 7, 8) The finding of a cyst accompanied by a reticular pattern of thin echoes is suggestive of hemorrhage (Fig. 2B). (6, 8) Dermoid cysts present with hyperechoic nodules within the mass with distal acoustic shadowing (Fig. 2C). (6, 8) Dermoid cysts are benign germ cells tumors, also called mature teratomas, and can contain various tissues such as hair, teeth and sebum. (6) Ultrasound can also be employed to characterize other common benign masses; endometrioma is a homogeneous, low echoic cyst without a solid component, but with a small echogenic focus on the inner wall of the cyst (Fig. 2D). (6, 7, 8) Leiomyomas, also called fibromas or fibroids, are benign smooth muscle tumors and appear as heterogeneous, hypoechoic, solid masses (Fig. 2E). (6, 7, 8) Cysts and masses are more likely to be malignant when they have the following features: solid non-hyperechoic component, nodularity or papillary structures, thickened septations, associated ascites in the rectouterine pouch, and high vascularity on Doppler (Fig. 2F). (4, 6, 8) Masses exhibiting these features are often associated with ovarian or uterine tube malignancy. (6, 8)

3.4 | International Ovarian Tumor Analysis (IOTA) – Simple rules

The IOTA group developed a model of simple rules to help distinguish benign and malignant masses on sonography. The IOTA model is useful to all physicians and is more specific and sensitive than other predictive tools like the RMI. The simple rules are comprised of 5 features that are suggestive of a malignant mass (M-features) and 5 features that are suggestive of a benign mass (B-features). M-features include:

M1 – irregular solid tumor

M2 – presence of ascites

M3 – presence of 4+ papillary structures

M4 – irregular multilocular solid tumor with a diameter

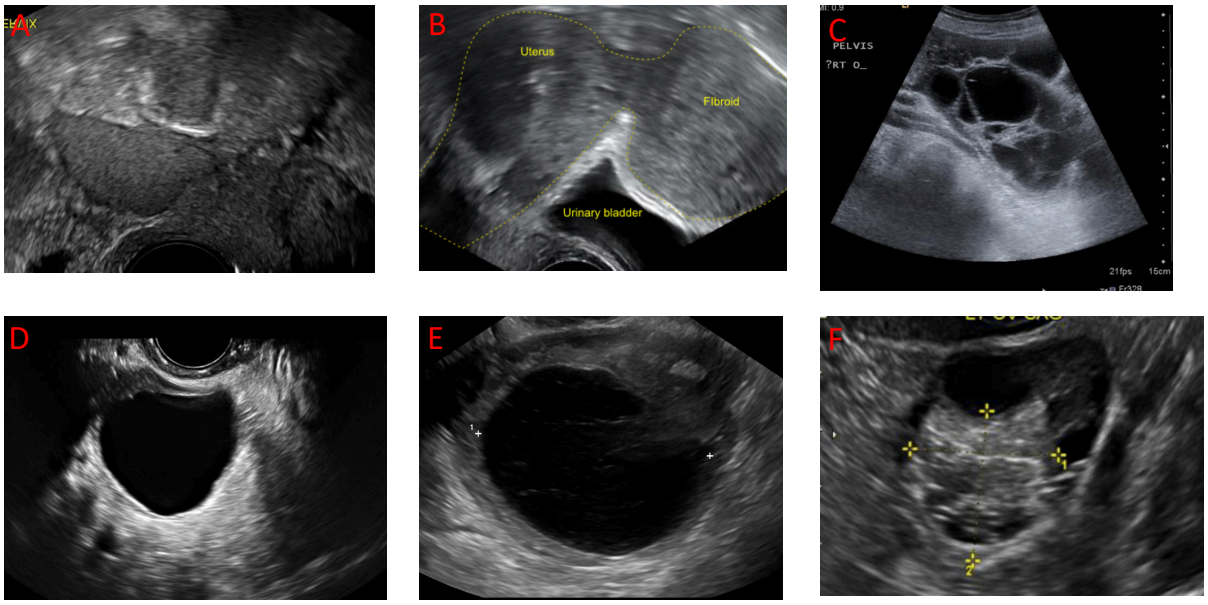

FIGURE 2

A. Simple cyst: thin-walled, no septations, unilocular, fluid-filled. Reproduced with permission of the Cleveland Clinic Center for Continuing Education. Ross E, Fortin C. Ovarian Cysts. Disease management (http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/ovarian-cysts/). ©2000-2020 The Cleveland Clinic Foundation. All rights reserved.

B. Hemorrhagic cyst: reticulated pattern within the cyst. https://upload.wikimedia.org/wikipedia/commons/3/35/Haemorrhagic_ovarian_cyst_ultrasound.jpg

C. Dermoid cyst (mature teratoma): hyperechoic nodules, acoustic shadowing, presence of abnormal tissue (fat, hair, sebum, teeth, etc...). Reproduced with permission of the Cleveland Clinic Center for Continuing Education. Ross E, Fortin C. Ovarian Cysts. Disease management (http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/ovarian-cysts/). ©2000-2020 The Cleveland Clinic Foundation. All rights reserved.

D. Endometrioma : homogeneous, low to medium echoic, no solid component or nodules. Reproduced with permission of the Cleveland Clinic Center for Continuing Education. Ross E, Fortin C. Ovarian Cysts. Disease management (http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/ovarian-cysts/). ©2000-2020 The Cleveland Clinic Foundation. All rights reserved.

E. Subserosal pedunculated uterine fibroid: heterogeneous, hypoechoic, solid. https://commons.wikimedia.org/wiki/File:Subserosal_uterine_fibroid.png

F. Ovarian cyst: multilocular, non-hyperechoic solid areas, thick septations, ascites, other potential masses. Strong suspicion for malignancy. Reproduced with permission of the Cleveland Clinic Center for Continuing Education. Ross E, Fortin C. Ovarian Cysts. Disease management (http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/womens-health/ovarian-cysts/). ©2000-2020 The Cleveland Clinic Foundation. All rights reserved.

100mm

M5 – high vascularization (Doppler score of 4).

B-features include:

B1 – unilocular cyst

B2 – presence of solid components with a diameter <7mm

B3 – presence of acoustic shadows

B4 – smooth multilocular tumor with a diameter <100 mm

B5 – no vascularization (Doppler score of 1) (Fig. 3).

FIGURE 3 International Ovarian Tumor Analysis simple rules
as seen at https://www.iotagroup.org/education/educational-material

If a mass has one or more B-features and no M-features, the mass is classified as benign. Alternately, a mass with one or more M-features and no B-features is classified as malignant. Up to 25% of masses are indeterminate, meaning that both B-features and M-features are present or that none of the rules apply. Indeterminate masses should be reassessed by an expert sonographer and malignant masses should be immediately referred to a gynecological-oncologist. (4)

3.5 | Risk of Malignancy Index I (RMI)

RMI I is currently used as a clinical prediction rule for malignancy risk evaluation of an adnexal mass. (1, 3, 5) It is comprised of three variables: ultrasound (U), menopausal status (M) and serum CA-125. (5) Ultrasound findings such as multilocular cysts, solid areas, metastases, ascites and bilateral lesions are taken into consideration. (1, 5) Absence of these characteristics corresponds to U=0, one finding corresponds to U=1 and two to five findings corresponds to U=3. M is the menopausal status; pre-menopausal is denoted by M=1 and post-menopausal is denoted by M=3. (1, 5) The final variable directly represents CA-125 serum concentration in units/mL. (1, 5) In order to obtain the RMI, all three variables must be multiplied (1, 5); for example, a post-menopausal woman with bilateral multilocular ovarian cysts and a CA-125 of 49 units/mL would obtain an RMI I score of U(3) x M(3) x CA-125(49) = 441. The cutoff for referral to an oncologist is for any RMI 250. (1, 5) However, many physicians refer when the RMI 200 due to a high suspicion of malignancy and the necessity of performing more targeted investigations. (1, 5)

4 | BEYOND THE INITIAL APPROACH

This section covers the most common diagnoses, the ones not to miss, and their basic management.

4.1 | Functional Cysts

Functional cysts are by far the most common diagnosis. (1) They are physiological and will often spontaneously resolve, which is why they are said to be “functional” or “organic”. (1, 8) They include follicular cysts, hemorrhagic cysts, corpus luteal cysts, and theca-lutein cysts. (1, 2) Cysts with a classic benign presentation should be followed on ultrasound in 8 to 12 weeks and then yearly for up to 5 years or until resolution. (9) Their associated risk of malignancy is extremely low, but a cyst that hasn’t resolved, has developed malignant features, or has grown over more than 6 months should raise suspicion and may require further investigations. (1, 2, 3, 9)

4.2 | Ovarian Cancer

Ovarian cancer is the second most common gynecological malignancy. (1) There is no screening for ovarian cancer and it is often discovered during the later

stages at which it becomes symptomatic. (1,10) 90% of ovarian cancer are epithelial carcinomas for which CA-125 is the main identified biomarker. (1) RMI I results can point to ovarian malignancy but diagnosis should always be confirmed by biopsy, either laparoscopic or image-guided. (10) The prognosis depends on the type of cancer, its stage, and grade. (1) In mild cases, surgical debulking and lymph node sampling are common therapeutic strategies. (1) However, total hysterectomy and bilateral salpingo-oopherectomy are almost always recommended, sometimes accompanied by adjuvant chemotherapy of carboplatin and paclitaxel. (1, 10) It is crucial to mention that ovarian cancer can be associated with a BRCA1/BRCA2 mutation, as well as hereditary nonpolyposis colorectal cancer, and that genetic testing might be advisable in patients presenting with a family history compatible with these cancers. (1)

4.3 | Tubo-Ovarian Abscess (TOA)

A TOA is an inflammatory fallopian mass often accompanied by symptoms such as fever, nausea, vomiting, and purulent discharge. (1, 11) They are most common in reproductive age patients and are a complication of pelvic inflammatory disease (PID), which is often caused by sexually transmitted pathogens or bacterial vaginosis-related pathogens. (11) PID is an acute infection of the upper genital tract and thus should be treated with an antibiotic regimen that usually includes Cefotetan IV and Doxycycline IV/PO. (11) If the patient is found to be unresponsive to therapy, drainage and surgery should be considered. (11)

4.4 | Adnexal Leiomyomas

Leiomyomas, or fibroids, are benign neoplasms arising from smooth muscles. (12) They can be found in the uterus or in the broad ligament. (12) They are usually asymptomatic unless they are large (bloating, compression, pain) or intra-uterine (menorrhagia, dysmenorrhea). (1, 12) The pain can be treated with NSAIDs and the patient may be prescribed oral contraceptives. (12) Surgical treatments are also available for the symptomatic patient, including uterine artery embolization, and in extreme cases, myomectomy or hysterectomy. (12)

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APPROACH TO
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Ischemic Stroke

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ABSTRACT

An approach to managing acute ischemic stroke includes recognition, investigations, treatment, and secondary prevention. Firstly, facial drooping, limb weakness and slurred speech are some common signs that should raise the suspicion for stroke. Upon presentation, investigations, including the national institute of health stroke scale and a CT head, should be done to rule out intracranial hemorrhage and diagnose an ischemic stroke. The treatment principles for an acute ischemic stroke focus on removing or dissolving the occlusion to maintain or reinstate perfusion of the brain. Finally, patients suffering ischemic stroke should be admitted to the acute stroke unit and monitored for complications. Basic medical management of comorbidities should also be considered to prevent subsequent ischemic episodes. This article will explain each of these processes in more detail to help develop a basic approach to the management of an acute ischemic stroke.

KEYWORDS
Ischemic stroke, Infarction, Neurology

1 | QUESTION

Mr. Smith is a 72-year-old right-handed man who presents to the emergency room with sudden-onset right-sided weakness and numbness, as well as impaired speech. His partner drove him to the hospital when they noticed his smile was asymmetrical (right-sided facial weakness) and he could not lift his right arm. His past medical history includes type 2 diabetes and hypertension. His medications include metformin 850 mg, ASA 81 mg, atorvastatin 40 mg and lisinopril 10 mg. Vital signs are evaluated; heart rate: 123 beats per minute (bpm), respiration rate: 22 breaths per minute, blood pressure 172/91 mmHg, temperature 37.9 C. Physical exam reveals diffuse right arm weakness (MRC grade 2), and the right biceps and brachioradialis deep tendon reflexes are graded as 3+. Right plantar response is extensor. Language assessment reveals deficits in fluency, comprehension, repetition, and naming.

Investigations

EKG: rapid atrial fibrillation at 118 bpm
CBC and basic metabolic panel: WBC 7.8 x 10^9/L, Hgb 130 g/L, platelets 250 x 10^9/L, Na 140 mmol/L, Cl 10^9 mmol/L, HCO_3 25 mmol/L, Creatinine 58 umol/L, urea 15 mmol/L, random blood glucose 8.4 mmol/L , INR 1.1
NIHSS evaluation: pending

Occlusion of which blood vessel would elicit the neurological symptoms presented above?

A. left anterior cerebral artery
B. basilar artery
C. right middle cerebral artery
D. left middle cerebral artery
E. left posterior cerebral artery

2 | ANSWER

D. Mr. Smith presented with acute onset right-sided weakness and numbness in his arm and face, as well as brisk right-sided upper limb reflexes on physical exam. These signs and symptoms are suggestive of a left hemisphere upper motor neuron lesion. Furthermore, his language deficits are indicative of a global aphasia with both expressive (i.e. producing language) and receptive (i.e. understanding language) components, localizing to the language areas of the left frontal (Broca's area) and temporal-parietal (Wernicke's area) lobes. The presence of cortical signs (aphasia), right upper motor neuron signs (weakness and hyperreflexia), and right-sided sensory symptoms (numbness) makes the most probable localization the left cerebral cortex, supplied by the left middle cerebral artery, making it the most likely vessel to be occluded. Anterior cerebral artery occlusions more often present with contralateral lower limb weakness and numbness. A basilar artery occlusion can result in "locked-in" syndrome, in which an individual is aware, but unable to communicate or move due to paralysis of most voluntary muscles in the body. Right middle cerebral artery occlusions present with left-sided sensory and motor symptoms, as well as neglect syndromes. Finally, a left posterior cerebral artery occlusion would more likely manifest as right-sided homonymous hemianopsia.

3 | INITIAL APPROACH

Stroke is a time-sensitive diagnosis potentially resulting in a myriad of long-term functional deficits. It is a leading cause of disability in Canada, affecting over 400,000 individuals. (1) In acute ischemic stroke, "time is brain", as treatment options and prognosis are both time-sensitive. In fact, complete occlusion of blood flow may lead to the death of vulnerable neurons after only 5 minutes. (2) It is therefore imperative that individuals have a practical approach to ischemic stroke, from recognition to recovery. The following article will describe such an approach at a level appropriate for those with basic clinical knowledge.

Basic management consists of timely recognition, diagnosis, and treatment, including 1) acute intervention (thrombolytic therapy and/or mechanical thrombectomy), 2) medical management in an acute stroke unit, and 3) secondary prevention measures and long-term follow-up. Each of these components will be briefly reviewed in the following sections.

3.1 | Recognition

Though this paper will focus primarily on medical intervention, it is important to acknowledge the role of public health interventions for greater awareness and timely recognition. Such interventions depend on the participation of the public and medical professionals to succeed. For example, public health messaging such as the "FAST signs of stroke" campaign launched by the Heart and Stroke Foundation have been employed to hasten treatment and improve health outcomes. (4) The F.A.S.T. acronym stands for: Face – is it drooping? Arms – can you raise both? Speech – is it slurred or jumbled? Time – time to call 911 right away. (4) Indeed, in a time series evaluation of the FAST campaign in England, authors noted a significant positive impact on information-seeking behaviour and emergency admissions. (5)

3.2 | Diagnosis

Initial evaluation of a suspected acute ischemic stroke consists of both good history taking, including time of onset and baseline functional status, and a focused neurological examination, often using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS

is a quantitative measure of stroke-related neurological deficit and is used to predict stroke severity and long-term outcome. (6) The scale evaluates level of consciousness, gaze, visual fields, facial palsy, motor strength, ataxia, sensation, language, dysarthria, and extinction/inattention in individuals showing signs of ischemic stroke. Upon confirmed suspicion of ischemic stroke, a non-contrast computed tomography (CT) scan is then ordered to rule out intra-cranial hemorrhage (ICH). A confirmed suspicion (from history and neurologic exam) along with a non-contrast CT with no evidence of ICH and no other explanation for the neurological deficits is sufficient to diagnose an acute ischemic stroke. Additionally, patients presenting with clinical suspicion for middle cerebral artery (MCA) stroke should be assigned an Alberta Stroke Program Early CT Score (ASPECTS) to quantitatively evaluate the degree of ischemic change on CT. (7) The score subtracts a point from a total score of 10 for each defined cortical region found to have evidence of early ischemic change. A score >8 suggests that patients may have a better chance for independence post stroke. (7)

3.3 | Thrombolytic Therapy

After the diagnosis of an acute ischemic stroke has been made, patients eligible to receive a tissue plasminogen activator (TPA) such as alteplase should receive treatment as soon as possible. (3, 8, 9) Intravenous (IV) alteplase should be dosed at 0.9mg/kg (not to exceed 90mg total dose), 10% given as a bolus and the remainder infused over 60 minutes. IV alteplase is administered to patients who have a blood pressure of less than 185/110 mmHg and do not fulfill any of the contraindications listed in Table 1, within 4.5 hours of stroke onset. (3) If blood pressure exceeds 185/110 mmHg, agents such as labetalol or nicardipine could be considered prior to TPA therapy. Importantly, obtaining blood work including troponins and INR should not delay administration of TPA, as long as there is no reason to suspect a coagulopathy. (3, 9) Also note that TPA should be administered even if mechanical thrombectomy is being considered. (3)

3.4 | Mechanical Thrombectomy

A CT angiogram should be performed at the same time as the diagnostic non-contrast CT to help determine eligibility for mechanical thrombectomy. Indications for

Contraindications for Tissue Plasminogen Activator Therapy
Extensive regions of clear hypoattenuation on CT
Intracranial hemorrhage identified on CT
Prior ischemic stroke within 3 months
Severe head trauma within 3 months
Post-traumatic infarction occurring during acute in-hospital treatment
Intracranial or spinal surgery within 3 months
History of intracranial hemorrhage
Symptoms and signs of subarachnoid hemorrhage
Gastrointestinal malignancy or bleed within 21 days
Platelets <100 000/mm3, INR >1.7, aPTT >40 seconds, PT >15 seconds
Received a full treatment dose of low molecular weight heparin within 24 hours
Infective endocarditis
Aortic arch dissection
Intra-axial neoplasm
Concomitant abciximab or IV aspirin (ASA not administered within 90 minutes)

INR, international normalized ratio; aPTT, activated partial thromboplastin time; PT, prothrombin time; ASA, acetylsalicylic acid

TABLE 1 Contraindications for tissue plasminogen activator therapy

mechanical thrombectomy include: a large vessel occlusion of the internal carotid or proximal middle cerebral arteries, less than 6 hours since symptom onset (2), age over 18, NIHSS score greater than 6, and no baseline neurological disability. (10) If patients present between 6 and 24 hours of symptom onset with anterior circulation occlusion, they may still be eligible for mechanical thrombectomy based on the result of a CT perfusion, diffusion-weighted magnetic resonance image (MRI), or MR perfusion scan. (10, 11) These studies measure blood flow to areas of the brain to help identify regions that have not yet been irreversibly damaged (the penumbra) and may benefit from reperfusion. (12) The mismatch ratio (MMR), which refers to the volume difference between the penumbra and the ischemic core, may be applied to predict response to reperfusion therapy; MMR >1.2 may predict greater response. (13)

3.5 | Medical Management

Patients should then be admitted to the acute stroke unit, where the focus is on avoiding complications. During this time, blood pressure should be monitored and kept under 180/105 mmHg in those who received thrombolytic therapy to minimize the risk of a hemorrhagic event. Those ineligible for thrombolytic therapy should not undergo intervention for elevated blood pressure unless exceeding 210/120 mmHg. (14) Furthermore, all patients should be administered dual antiplatelet therapy within 24-48 hours (therapy should be held 24 hours in those who received TPA) to prevent recurrent thrombosis and ischemia. Brain imaging should also be repeated at 24 hours to assess the risk of hemorrhage. (3) Patients should also be kept nil per os (NPO) until assessed for dysphagia by a certified clinician or speech language pathologist. (3) Bed rest for only the first 12 hours after admission is recommended, as recent findings suggest that 12 (as opposed to 24) hours of bedrest is associated with significant reductions in pneumonia rates, discharge NIHSS scores, and length of stay. (15)

3.6 | Secondary Prevention

As previously mentioned, all patients should be started on dual antiplatelet therapy and/or anticoagulation. (3) Patients who have suffered mild to moderate ischemic stroke who receive a combination of aspirin and clopidogrel have a lower risk of future major ischemic events over 90 days than those treated with aspirin alone. (16) As most recurrent ischemic events occur within the first week, dual antiplatelet therapy is recommended to be started within 24-48 hours and continued for at least 21-30 days post-ischemic stroke. (12) After this time, clopidogrel may be removed and while aspirin is continued indefinitely. (3) Anticoagulation should be reserved for those with identified atrial fibrillation or cardioembolic risk factors. Finally, secondary prevention should be addressed through the management of hypertension, dyslipidemia, and hyper/hypoglycemia during admission. Patients should also be given education regarding smoking cessation, physical activity, and nutrition before discharge. (3)

4 | BEYOND THE INITIAL APPROACH

This section will discuss various mechanisms of ischemic stroke including embolism, decreased perfusion, and thrombosis. Understanding the major mechanisms by which ischemic stroke develops may guide secondary prevention through the reduction of pertinent risk factors.

4.1 | Embolism

Embolism to the brain may affect both large and small cerebral vessels, leading to an acute ischemic stroke. The source of an embolus to the brain may be cardiac or arterial in origin, with left ventricular thrombi being an especially common source. Atrial fibrillation is an independent risk factor for cardioembolic stroke, regardless of its duration. Those with suspected cardioembolic stroke should therefore receive an echocardiogram for investigation of atrial fibrillation and subsequently be

treated with oral anticoagulation to an optimal INR of 2.0 to 3.0. (17, 18) Note that anticoagulation in a patient with atrial fibrillation and acute cardioembolic stroke carries a risk of hemorrhage. For this reason, anticoagulation should be delayed several days in those with low risk of recurrence. In those with high risk of recurrence, especially if the infarct is not large and the patient does not have uncontrolled hypertension, early anticoagulation is still recommended. (17)

4.2 | Perfusion Deficit

Acute ischemic stroke may also be due to stenosis of large and small cerebral vessels leading to perfusion deficits, with atherosclerotic plaques being a major factor in the development of vessel stenosis and occlusion. Regarding large artery atherosclerotic plaques, stenoses resulting in occlusion of more than 70% identified with angiography predispose individuals for ischemic events, including thrombo-embolic complications. Medical and surgical interventions available for these patients include anticoagulation (as described above) and carotid endarterectomy, respectively. Hypoperfusion of small (lacunar) arteries is another important source of acute ischemic stroke. Lacunar strokes are due to occlusion of small, deep, perforating arteries in cerebral circulation and often present with isolated motor or sensory deficits. Etiology may be due to cardiac or arterial embolism, plaque embolism, or even large vessel stenosis. In fact, lacunar hypoperfusion may be a first indication of large vessel stenosis. Measures to reduce atherosclerotic risk factors are therefore beneficial for secondary and primary prevention of vessel stenosis that causes acute ischemic stroke. (17) Lifestyle modifications including regular exercise, smoking cessation, and adequate nutrition are particularly pertinent in preventing atherosclerotic plaques that arise from hypertension, dyslipidemia, and hyperglycemia. (18)

4.3 | Thrombosis

Thrombosis (and prothrombotic states) is another important mechanism of acute ischemic stroke. Thrombosis may be secondary to atherosclerotic plaque rupture, or primary due to hematological abnormality. In the case of atherosclerotic plaque rupture, medical management of the atherosclerotic risk factors described above may be helpful in secondary prevention. Primary prothrombotic states due to hemostatic abnormalities in antithrombins, heparin cofactor II, proteins C and S and fibrinolytic factors may be associated with stroke at any age, and in these patients long-term anticoagulation with warfarin is generally recommended. (17, 18)

5 | CONCLUSION

In acute ischemic stroke, quick and efficient recognition and activation of the multidisciplinary team are critical for timely treatment. Upon emergency room arrival, stroke severity should be estimated based on the NIHSS, and hemorrhagic stroke should be ruled out based on non-contrast CT. After the diagnosis of acute ischemic stroke, TPA should be administered within the first 4.5 hours. If the stroke is identified as a large vessel occlusion, mechanical thrombectomy should be considered within the first 6-24 hours. Finally, stroke patients should be started on dual anti-platelet therapy and admitted to the hospital for additional investigations and management. Elucidation of the stroke etiology may aid in guiding additional investigations and secondary prevention.

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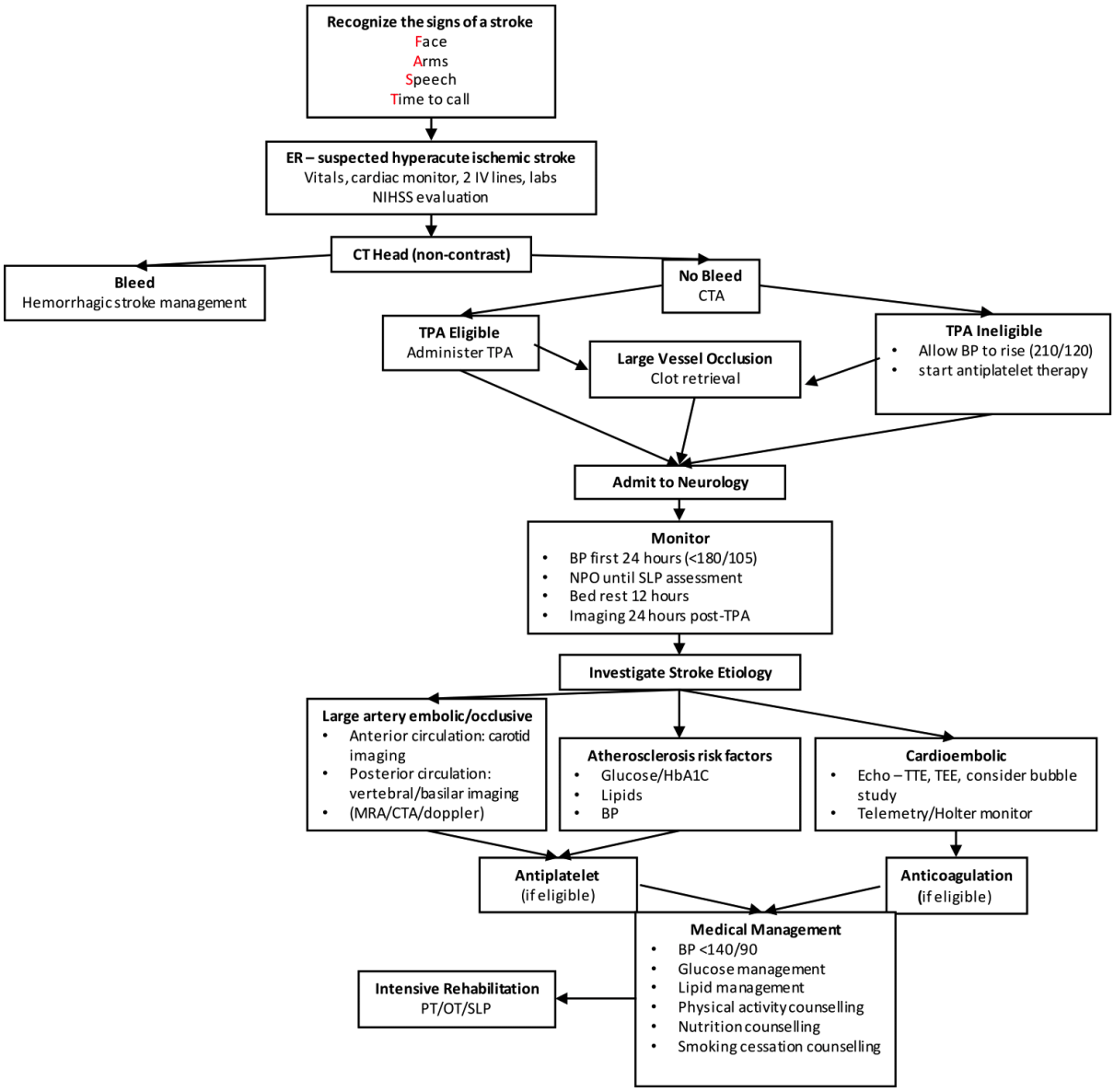
6 | TABLES & FIGURES



FLOWCHART 1 Approach to Ischemic Stroke

ER, emergency room; NIHSS, national institute of health stroke scale; CT, computed tomography; CTA, computed tomography angiography; TPA, tissue plasminogen activator; BP, blood pressure; NPO, non-per-oral; MRA, magnetic resonance angiography; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; PT, physical therapy; OT, occupational therapy; SLP, speech-language pathologist.

APPROACH TO
McGill Journal of Medicine

Delirium

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ABSTRACT

Delirium is a common and serious geriatric syndrome with core features of acute onset and inattention. This syndrome is often underdiagnosed and is associated with many adverse outcomes, such as prolonged hospitalization, institutionalization, functional impairment and death. This review summarizes an approach to the recognition, work-up, management and prevention of delirium.

KEYWORDS
Delirium

1 | QUESTION

An 82-year-old woman is admitted with a hip fracture. Past medical history is remarkable for hypertension, for which she takes amlodipine and perindopril, and occasional constipation. She lives at home with her partner and is independent for all her activities of daily living. Her intraoperative course is unremarkable, but on postoperative day 2 she develops agitation and confusion. Her vital signs are notable for a blood pressure of 160/100 mmHg and tachycardia of 105 bpm, the other findings in a limited physical exam are normal. Her complete blood count, serum electrolytes and urinalysis are normal this morning.

Which intervention is considered first-line in this situation?

A. Physical restraints
B. Haloperidol
C. Quetiapine
D. Analgesics
E. Diazepam

2 | ANSWER

D. The initial management for delirium involves addressing the underlying condition and utilizing non-

pharmacologic interventions. In this case, once life-threatening conditions are ruled out, uncontrolled pain likely precipitated the patient's delirium (1). However, caution needs to be taken when using analgesics in older adults; scheduled adjuvant treatments should be used to minimize the use of opioids (2). The use of physical restraints should be limited as this is associated with an increased risk of injury (3). Antipsychotic medications such as haloperidol and quetiapine should only be considered if distressing symptoms or dangerous behaviour is present and if non-pharmacologic measures have failed (2,4). Benzodiazepines such as diazepam have consistently been associated with poorer outcomes in older adults and, in general, should only be used in cases of alcohol withdrawal or if the patient has a history of neuroleptic malignant syndrome and therefore cannot take antipsychotics (2).

3 | INITIAL APPROACH

3.1 | Recognition of Delirium

Delirium was often described using a diverse range of terms such as "acute confusional state", "toxic metabolic encephalopathy" and "acute brain syndrome" (5). Over time, the definition has evolved to describe an acute and fluctuating syndrome of reduced awareness and inability to sustain attention, usually occurring in the setting of a medical condition (6). Though delirium typically develops over a short period of time, it can persist for weeks or even months, and it is "not better accounted for by a pre-existing, established, or evolving dementia" (7).

Risk factors for developing delirium include advanced age, regular administration of more than 5 medications, presence of cognitive or sensory impairments and presence of multiple co-morbidities (1).

Delirium is a clinical diagnosis and multiple scales have been developed to aid clinicians in recognizing this syndrome. A commonly used validated scale is the Confusion Assessment Method (CAM), which has a sensitivity of 94-100% and a specificity of 90-95% (8). The diagnosis of delirium by CAM requires the presence of acute onset with fluctuating course and inattention, and either disorganized thinking or an altered level of consciousness (Table 1). Inattention is commonly assessed using various bedside tests. Examples of such tests include: the digit span test—patients are asked to recall the sequence of numbers; reciting the months of the year and days of the week backward; and serial sevens—counting down from one hundred in sevens (9). Although these tests are helpful in diagnosing delirium, a positive response to the following: "Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?" is sufficient to diagnose delirium with the CAM model.

Delirium is often missed in a busy hospital setting, particularly if the patient is only seen briefly and happens to be in a lucid interval. Additionally, delirium can present with either hyperactive features such as restlessness, agitation, and hypervigilance; or hypoactive features such as lethargy and sedation (6). The fact that hypoactive delirium is more common that hyperactive delirium creates additional diagnostic challenges (10). Rates of unrecognized delirium, defined as delirium diagnosed by an expert assessor after the diagnosis was not made by the patient's treating physicians and nurses, are around 60% (11). Hence, clinicians and trainees should remain vigilant when the patient is described as "confused" or "not themselves" and gather collateral information from other healthcare professionals and family members. Delirium superimposed on dementia (DSD) poses another diagnostic challenge, since clinical phenotypes of some dementias show overlap with delirium. More research is needed to develop better tools for diagnosis of DSD (12).

3.2 | Identifying the Cause

Once delirium has been recognized, clinicians should aim to identify and treat the underlying etiology. The majority of recommendations for the evaluation and treatment of delirium are based on clinical observations and expert opinion since there are currently no laboratory or radiological studies available to confirm its pres-

ence and resolution (1).

There are various mnemonics and system-based approaches to help clinicians identify the precipitant of delirium. One commonly used mnemonic, DELIRIUM, is outlined in Table 2 (2). This mnemonic includes the following causes of delirium to consider: drugs; electrolyte and endocrine disturbances; lack of drugs, i.e. discontinuation of drugs; infections; reduced sensory input; intracranial disorders; urinary and fecal disorders; and myocardial and pulmonary disorders as causes of delirium to consider. Given a wide differential diagnosis and frequent "atypical" presentations of diseases in older adults, a clinician must develop a systematic approach to any patient experiencing delirium, as briefly summarized below.

3.2.1 | History

Clinicians should inquire as to: when the mental status changes first began; how they change throughout the day; and whether they are associated with other physical signs and symptoms, for example, tachypnea. A thorough review of medications, over the counter drugs, and other substances is required as well (2). Consideration should also be given to recently discontinued medications and substances that may cause withdrawal, such as alcohol or benzodiazepines.

3.2.2 | Physical Exam

Physical exam should include measurement of vital signs, hydration status, skin condition, and should evaluate for potential infectious foci. An examination of the cardiovascular, respiratory and abdominal systems should be performed. If possible, a neurological exam should be performed to evaluate for new focal findings (2).

3.2.3 | Laboratory Tests

Targeted testing based upon history and physical exam is appropriate in most cases, as desire for diagnostic completeness can increase costs, subject patients to unnecessary investigations and potentially delay the diag-

Features	Assessment
1. Acute onset and fluctuating course	Usually obtained from a family member or nurse and shown by positive responses to the following questions: "Is there evidence of an acute change in mental status from the patient's baseline?" and "Did the abnormal behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?"
2. Inattention	Shown by a positive response to the following: "Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?"
3. Disorganized thinking	Shown by a positive response to the following: "Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?"
4. Altered level of consciousness	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.
From Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec

TABLE 1 The Confusion Assessment Method (CAM)

nosis or more obvious disorders (13). However, a thorough review of all differential diagnoses should be performed, particularly to rule out life-threatening causes such as hypoglycemia and medication toxicities in a timely manner. Routine laboratory tests include a complete blood count, measurement of serum electrolytes, venous blood gas, liver-function tests, and urinalysis and urine culture (2). Chest radiograph, electrocardiogram, and troponins are also often helpful (2). Additional tests that may be required include screening for toxicology and specific drugs (e.g. digoxin, lithium); blood cultures; and more extensive imaging, for example, computed tomography of the head (2). Lumbar puncture and electroencephalography are rarely helpful unless there is a high clinical suspicion of meningitis or seizure activity, respectively (2).

3.3 | Management and Prevention

Management of delirium is a complex process that often requires interdisciplinary teams (2). Although the focus is on addressing the underlying cause such as a urinary tract infection or contribution from a medication, the prevention of complications and maintenance of patient comfort and safety are as important. Strategies to minimize complications include monitoring urine output and bowel movements, avoiding physical restraints, ensuring adequate dietary intake, and appropriate mobilization (2).

Non-pharmacologic interventions remain the cornerstone of delirium management, as most studies do not show benefit of antipsychotic medications on decreasing the duration and severity of delirium, and multiple studies demonstrate harm with the use of such medications (14). Some of the non pharmacological interventions include: correction of hearing and vision deficits; appropriate mobilization; improvement of sleep-wake cycles with exposure to daylight during the day and minimization of noise and disruptions during the nighttime; orientation activities; and avoidance of abrupt changes in patient's environment, for example, frequent room changes (15). Early efforts to restore function should include involvement of physical and occupational therapy specialists to optimize activities of daily living (2).

Family education can also be beneficial both to the patient and to the caregiver. For example, family education allows caregivers to recognize subtle changes in cognition, which can be helpful in the diagnosis of delirium. Close knowledge regarding the patient's needs, routines, and manifestations of discomfort can

Category	Examples to Consider
D – drugs	Newly initiated drugs, changed doses, interactions, including over the counter drugs
E – electrolyte and endocrine disturbances	Common imbalances include dehydration, sodium and calcium imbalance, and thyroid issues
L – lack of drugs	Recently discontinued medications and substances that can cause withdrawal symptoms or increased pain levels
I – infections	Urinary tract, respiratory tract, soft tissue, and device infections
R – reduced sensory input	Lack of hearing and vision aid
I – intracranial disorders	Strokes, bleeds, masses
U – urinary and fecal disorders	Urinary retention and constipation
M – Myocardial and pulmonary disorders	Myocardial infarcts, arrhythmias, hypoxia, hypercapnia

Adapted from Marcantonio ER. Delirium in Hospitalized Older Adults. New England Journal of Medicine. 2017 Oct 12;377(15):1456–66.

TABLE 2 Common Causes of Delirium

also be utilized to provide earlier detection and treatment. Furthermore, family can often help with non-pharmacological management, such as re-orienting the patient using familiar objects (15).

With increased awareness of how prevalent delirium is within the hospital settings, many interventions have been developed in attempts to prevent delirium. One of the most widely disseminated interventional programs is the Hospital Elder Life Program (HELP) (16). HELP uses trained volunteers to provide patients with individually assigned interventions such as (re-)orientation, cognitive activation, mobilization, meal companionship, and hydration. This program has been shown to significantly reduce the rates of delirium and prevent loss of functioning in hospitalized older adults (16,17).

4 | BEYOND INITIAL APPROACH

Pharmacologic therapies may sometimes be required for distressing sensory disturbances or behaviours that can pose danger to the patient or others (2). Low dose, short term therapy with haloperidol or an atypical antipsychotic (e.g. risperidone) can be considered, though the use of antipsychotics for management of delirium is considered an off-label indication in Canada (18). These drugs are contra-indicated in patients with Parkinson disease, Lewy body dementia, and history of neuroleptic malignant syndrome. Such agents can significantly worsen parkinsonism and cognitive impairment and significantly increase the risk of mortality (19).

Benzodiazepines are considered second-line agents and should only be used in cases of alcohol withdrawal or if the patient has a history of neuroleptic malignant syndrome and therefore should not take antipsychotics (2). Large studies have consistently showed poor outcomes associated with benzodiazepine use in older adults (20).

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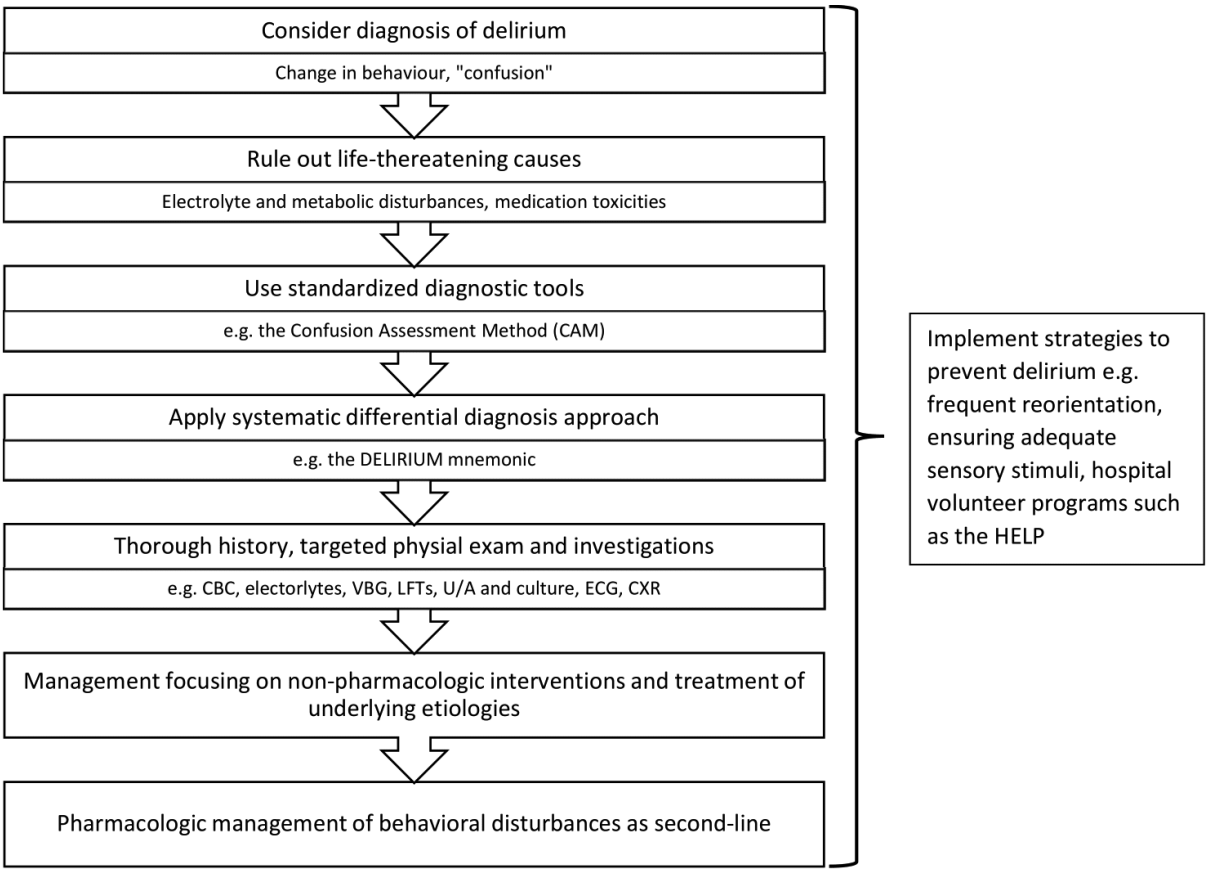
5 | TABLES & FIGURES



FLOWCHART 1 Approach to Patient with Suspected Delirium

CBC - complete blood count, VBG – venous blood gas, LFTS - liver function tests, U/A - urinalysis, ECG - electrocardiogram, CXR – chest X-ray, HELP - Hospital Elder Life Program

APPROACH TO
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Hypercalcemia

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ABSTRACT

Hypercalcemia is a presentation commonly encountered in the clinical setting. Due to its vast differential diagnosis, a systematic approach is necessary when approaching patients with hypercalcemia. This article presents a simple, yet thorough approach to help clinicians determine the etiology of their patients' hypercalcemia. The main components of history taking, physical examination, and laboratory investigations for patients with hypercalcemia are highlighted. Emphasis is put on the importance of determining whether the hypercalcemia is associated with elevated or inappropriately normal parathyroid hormone (PTH) levels or not. The main etiologies of PTH-dependent hypercalcemia and PTH-independent hypercalcemia are explored. Primary hyperparathyroidism and hypercalcemia secondary to malignancy are highlighted as together, they make up 90% of hypercalcemia cases. A presentation of the management principles of hypercalcemia is also provided.

KEYWORDS
Ionized calcium, Total calcium, Malignancy-associated hypercalcemia, Hyperparathyroidism, Hypercalcemia.

1 | QUESTION

A 57-year-old female presents to your family medicine clinic for the first time after being told her calcium levels were elevated (2.78 mmol/L) at a recent emergency room visit for a migraine headache. No other abnormalities were noted on her complete blood count, electrolytes, and renal function tests at the time. She is known for migraines, osteoarthritis, hypertension, and dyslipidemia. Her medications are atorvastatin 20 mg PO DIE and amlodipine 5 mg PO DIE. On history, she describes feeling well at the time of her visit and denies having any family members with calcium abnormalities. She reports occasional bilateral knee pain, which she attributes to her osteoarthritis. Her vital signs are stable and her physical exam is unremarkable.

Among the following, which would you send as part of your initial investigations for this patient?

A. Serum protein electrophoresis (SPEP)
B. Parathyroid hormone (PTH)
C. 24-hour urine collection for calcium and creatinine
D. PTH-related peptide (PTHrP)
E. Chest radiograph

2 | ANSWER

B. Initial investigations for hypercalcemia should include a repeat total and ionized calcium to confirm the diagnosis of hypercalcemia. Albumin levels should also be ordered since abnormally low albumin levels may affect the total serum calcium level measured. Most physicians will also order extended electrolytes, renal function tests, and a complete blood count. One of the most important initial investigations is the serum PTH level as depending on whether it is normal/high or low, the differential diagnoses are very different. If the PTH is low, PTHrP (D), SPEP (A), and a chest radiograph (E) may be sent as part of a malignancy workup. If the PTH is normal or high, a 24-hour urine collection for calcium and creatinine (C) is often ordered to assess for familial hypocalciuric hypercalcemia (FHH). However, these would not be done prior to ordering a PTH.

3 | INITIAL APPROACH

3.1 | Clinical Assessment

During history taking of a patient with hypercalcemia, the focus should be on eliciting the signs and symptoms of hypercalcemia as well as its possible etiologies. The clinical manifestations of hypercalcemia can be remembered by the mnemonic "stones, bones, abdominal moans, and psychic groans", which refers to its renal, skeletal, gastrointestinal, and neuromuscular manifestations. Psychiatric and cardiovascular manifestations can also occur. These are detailed in Table 1. It is important to remember that patients with mild hypercalcemia, defined as values not exceeding 0.25 mmol/L above normal range or <3 mmol/L, may be asymptomatic (1-3).

Since hypercalcemia may be due to multiple etiologies, performing a thorough review of medications, family history, and past medical history is essential. For example, clinicians should review the patient's medications for drugs that could cause hypercalcemia. Moreover, a family history of hypercalcemia might suggest a genetic mutation resulting in hypercalcemia (1). Clinicians should also inquire about clinical features suggestive of various cancers as well as the patient's most recent cancer screenings since malignancy is a known etiology of hypercalcemia (2). Lastly, the patient's past medical history can reveal medical conditions associated with hypercalcemia such as endocrine disorders, granulomatous diseases, or kidney disease (2).

3.2 | Initial Laboratory Investigations

Hypercalcemia is defined as a serum calcium level greater than two standard deviations above the normal mean in a reference laboratory. Hypercalcemia should be confirmed with repeat measurements of ionized cal-

Mnemonic	Manifestations
"Stones": Renal manifestations	Nephrolithiasis, nephrogenic diabetes insipidus, polydipsia, polyuria, dehydration.
"Bones": Skeletal manifestations	Bone pain, arthritis, osteoporosis, osteitis fibrosa cystica in hyperparathyroidism.
"Abdominal moans": Gastrointestinal manifestations	Nausea, vomiting, anorexia, constipation, abdominal pain, pancreatitis, peptic ulcer disease.
"Psychic groans": Neuromuscular manifestations	Impaired memory, confusion, lethargy, stupor, coma, muscle weakness.
Psychiatric manifestations	Irritability, depression, anxiety, hallucinations, psychosis.
Cardiovascular manifestations	Shortened QT interval, arrhythmias, bundle branch block, bradycardia, syncope.

Adapted from (1) and (3).

TABLE 1 Clinical manifestations of hypercalcemia.

cium and total calcium. However, it is important to account for biologic and analytic variation when interpreting repeat measurements to determine if one value is truly different from the other and if a value is significantly elevated (4). Although the reference values can vary depending on the laboratory, normal total calcium generally ranges between 2.15-2.60 mmol/L and ionized calcium usually ranges between 1.17-1.33 mmol/L (1). Low albumin levels may also affect total serum calcium level (1). However, the single most important investigation for hypercalcemia is the PTH level. Hence, we will divide the different diagnoses for hypercalcemia depending on if the PTH is normal or high (PTH-dependent hypercalcemia) or if the PTH is low (PTH-independent hypercalcemia). Although the causes of hypercalcemia are numerous, 90% of all cases of hypercalcemia result from primary hyperparathyroidism or malignancy (1).

3.3 | PTH-Dependent Hypercalcemia

In PTH-dependent hypercalcemia, PTH is inappropriately normal or high despite elevated calcium levels. The most common cause is primary hyperparathyroidism. 80% of these cases result from a single parathyroid adenoma. It can also be associated with hyperplasia of the parathyroid glands. Often, patients presenting with mild asymptomatic hypercalcemia will be found to have primary hyperparathyroidism (1).

Primary hyperparathyroidism can be distinguished from familial hypocalciuric hypercalcemia (FHH) by performing a 24-hour urine collection for calcium and creatinine. FHH is associated with a low calcium to creatinine clearance ratio (< 0.01) whereas primary hyperparathyroidism would lead to a high ratio (>0.02). For practical purposes, urinary calcium to creatinine ratio or calcium concentration in a spot urine sample is often used for the initial evaluation of calciuria. If clinically indicated, calciuria can be confirmed with a 24-hour urine collection. FHH is an autosomal dominant condition caused by a calcium-sensing receptor gene mutation. It is important to distinguish between FHH and primary hyperparathyroidism as the management differs significantly. For example, parathyroidectomy is not appropriate for FHH (5). However, FHH is rare and usually benign. Hence, when faced with PTH-dependent hypercalcemia in clinical practice, physicians will often focus on ordering imaging studies of the parathyroid to assess for adenoma rather than the 24-hour urine collection.

Moreover, primary hyperparathyroidism may be a presentation of multiple endocrine neoplasia type 1 (MEN 1) syndrome, where parathyroid hyperplasia or adenoma occurs with pituitary and pancreatic islet tumors. It is also associated with MEN 2A syndrome, which is characterized by medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia or adenoma. Hence, it is important to inquire about these associated conditions in such patients as well as perform a thorough family history. As these syndromes are hereditary, genetic testing is usually performed if there is a high clinical suspicion (5).

Other causes of PTH-dependent hypercalcemia include tertiary hyperparathyroidism. It occurs in patients with end-stage renal disease resulting in prolonged secondary hyperparathyroidism, high phosphate, and low vitamin D. Over time, this leads to autonomous PTH secretion unresponsive to plasma calcium levels. The drug lithium can also cause PTH-dependent hypercalcemia, which may be reversed if the drug is discontinued (3).

3.4 | PTH-Independent Hypercalcemia

In PTH-independent hypercalcemia, PTH is appropriately suppressed from high calcium levels.

Malignancy: Malignancy is a common etiology of hypercalcemia and can result from various mechanisms: osteolysis from metastases, excess PTH-related peptide (PTHrP), excess calcitriol production, and multiple myeloma (6). Hence, many clinicians will pursue investigations to search for an occult malignancy in PTH-independent hypercalcemia. PTHrP, alkaline phosphatase, calcitriol, and multiple myeloma workup are usually included as part of the laboratory investigations. In terms of imaging, a mammogram, chest radiograph, and abdominal CT are often done (2).

Osteolysis from metastasis: Bone metastases resulting in extensive osteolysis can result in hypercalcemia.

The most frequently associated malignancies are multiple myeloma and breast cancer. A clue to this etiology of malignancy-associated hypercalcemia is a high alkaline phosphatase level. Lytic lesions may also be seen on imaging (3).

Excess PTHrP: Some solid tumors secrete PTHrP. Although PTH is suppressed, PTHrP acts similarly to PTH by increasing bone resorption and calcium reabsorption in the kidney. It is most commonly associated with squamous cell carcinomas of the lung, head and neck, esophagus, skin, or cervix, and carcinomas of the breast, kidney, prostate, and bladder (7).

Excess calcitriol (1,25 dihydroxyvitamin D): Lymphomas may cause increased production of calcitriol as a result of their 1α-hydroxylase activity. The excess calcitriol subsequently leads to increased renal and gastrointestinal absorption of calcium. Hence, lymphoma patients may present with hypercalcemia (6).

Multiple myeloma: Multiple myeloma can also result in hypercalcemia due to bone lysis. It can be suspected if there is presence of other typical signs and symptoms of the disease: anemia, renal insufficiency, and bone pain. Serum and urine protein electrophoresis and serum free light chains are commonly ordered to investigate for multiple myeloma. Lytic lesions in the bone may also be seen on skeletal survey (8).

No evidence of malignancy: If no evidence of malignancy is found, other less common causes of PTH-independent hypercalcemia can be considered. These can be divided into the following categories: endocrinopathies, granulomatous diseases, drugs, and immobilization (1).

Endocrinopathies: Hypercalcemia can be associated with hyperthyroidism due to increased bone resorption (3). Although less common, adrenal insufficiency has also been reported as a cause of hypercalcemia (9). Although the mechanism of hypercalcemia in adrenal insufficiency is not entirely clear, it is thought that the hypovolemia associated with adrenal insufficiency results in decreased glomerular filtration rate. Hence, the amount of calcium filtered at the glomerulus is also decreased (9).

Granulomatous diseases: In granulomatous diseases, excess calcitriol is synthesized in macrophages and other cells in granulomas, which disturbs the usual production of calcitriol regulated by calcium, phosphate, and PTH levels. Consequently, it may result in hypercalcemia (5). Examples of granulomatous diseases include sarcoidosis, berylliosis, tuberculosis, fungal infections, and Crohn's disease (10).

Drugs: Thiazide diuretics are a common cause of drug-related hypercalcemia as they increase renal reabsorption of calcium. Around 8% of patients taking thiazides develop hypercalcemia (11). Moreover, ingestion of large amounts of calcium or calcium-containing antacids may result in milk-alkali syndrome, which is characterized by hypercalcemia, alkalosis, and renal failure (5). Excessive ingestion of Vitamin A and Vitamin D may also lead to hypercalcemia. Vitamin A is thought to stimulate osteoclastic resorption and inhibit osteoblastic formation (1).

Immobilization: Immobilization may rarely result in hypercalcemia due to decreased bone formation and increased bone resorption. This usually occurs in individuals with a high bone turnover such as in Paget's disease or in younger individuals (5).

4 | BEYOND INITIAL APPROACH

The management of hypercalcemia will depend on the underlying etiology. Mild hypercalcemia is defined as values not exceeding 0.25 mmol/L above normal range or <3 mmol/L (1). Most instances of mild hypercalcemia are from primary hyperparathyroidism. If it does not result in any symptoms (e.g., skeletal, renal, gastrointestinal, or neuromuscular), patients can usually be monitored without surgery (3). Indications for parathyroidectomy in primary hyperparathyroidism include overt clinical manifestations, calcium >0.25 mmol/L above normal, creatinine clearance <60 mL/min, low bone mineral density, history of fragility fracture, and age <50 years old (2). The management of hypercalcemia from other etiologies is beyond the scope of the current article.

Acute, severe hypercalcemia is defined as serum calcium greater than 3.5 mmol/L. However, indications for urgent treatment of hypercalcemia are more based on the clinical manifestations than the serum level. The

mainstay of management consists of aggressive intravenous fluids and intravenous bisphosphonate. Calcitonin is sometimes used as a temporizing measure. Furosemide, glucocorticoids, and dialysis can also be indicated in some patients (2).

In rare cases, severe hypercalcemia may result in confusion and decreased level of consciousness. Airway management is crucial in the care of such patients. It may also result in hemodynamic instability requiring fluid resuscitation. Moreover, it can induce arrhythmias. Hence, these patients should undergo an electrocardiogram. Hemodialysis against a low or zero calcium dialysate should be considered in these potentially life-threatening cases when significant cardiovascular or neurologic dysfunction is present (1).

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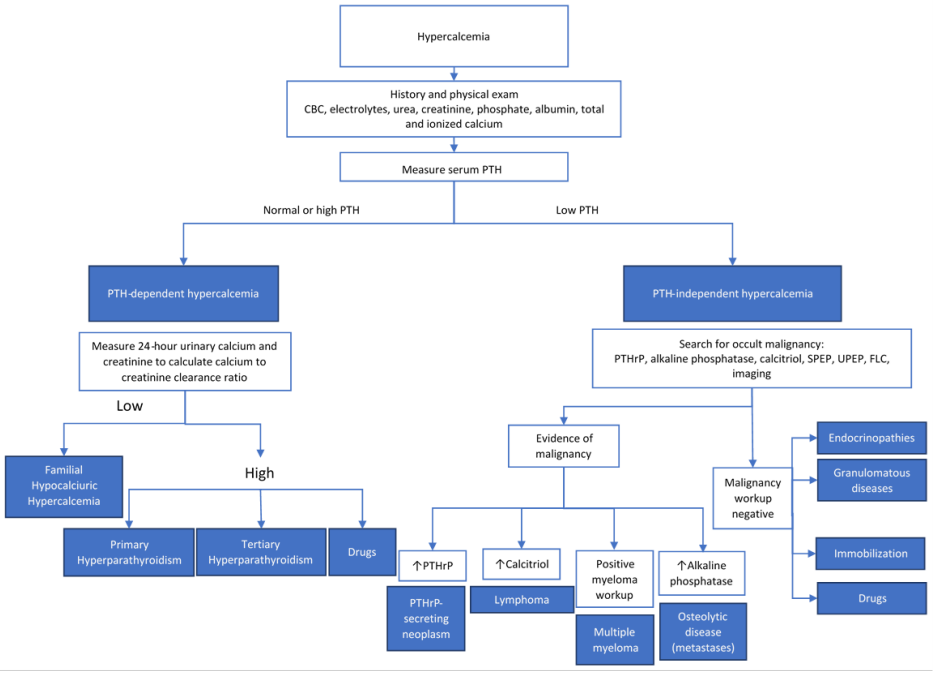
5 | FLOWCHARTS



FLOWCHART 1 Approach to hypercalcemia: Basic algorithm to determine the appropriate investigations and differential diagnoses of hypercalcemia.
CBC = Complete blood count, PTH = Parathyroid hormone, PTHrP = Parathyroid hormone-related peptide, SPEP = Serum protein electrophoresis, UPEP = Urine protein electrophoresis, FLC = Serum free light chains. Adapted from (2) and (12).

APPROACH TO
McGill Journal of Medicine

Shock

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ABSTRACT

Shock is a life-threatening pathophysiologic state referring to inadequate organ perfusion, which can progress to end-organ dysfunction and eventually, multiple organ failure and death. The diagnosis of shock is clinical, necessitating good understanding of the underlying etiology, pathophysiology, as well as the clinical, biochemical, and hemodynamic manifestations of the various presentations of shock. This article describes an approach to shock, highlighting the important initial actions, pertinent clinical findings, and the four main types of shock, and offers an overview of the inotropes and vasopressors used in the intensive care setting. A case study and additional figures are included to supplement the presented concepts.

KEYWORDS

Shock, Vasopressers, Inotropes, Cardiogenic shock, Neurogenic shock, Obstructive shock, Anaphylactic shock, Hypovolemic shock, Septic shock.

1 | QUESTION

A 54-year-old man was brought to the emergency department overnight following a motor vehicle accident. Although he was found to be neurologically intact, and examination of his head and extremities was largely unremarkable, an ultrasound examination revealed intra-abdominal free fluid. He underwent a laparotomy for a ruptured spleen.

He is otherwise not known for any past medical history (including allergies and alcohol/recreational drug use), and up until last night had been in his usual state of health. There is no notable family history.

The patient's post-operative recovery course is unremarkable until mid-morning, about 5 hours after his operation. He is found by his nurse to be less responsive, with a blood pressure drop from 136/90 to 89/55, an increase of his heart rate to 121, a temperature of 38.1^{o}C, and increased oxygen needs. On physical exam, his abdomen is soft, dressings are dry, and capillary refill is normal. His skin is warm to touch. His EKG indicates sinus rhythm, unchanged from his baseline. Stat labs are drawn, and first to result is his blood gas lactate, which is elevated from 2 hours ago. He rapidly deteriorates with disseminated intravascular coagulation (DIC).

Which type of shock would you consider most probable in this scenario?

A. Hypovolemic shock

B. Cardiogenic shock)
C. Septic shock
D. Anaphylactic shock
E. Neurogenic shock

2 | ANSWER

C. The most likely diagnosis in this scenario is septic shock. His presentation (fever, vasodilation, DIC) is consistent with septic shock, and the history of abdominal surgery and trauma suggests a potential source of infection: gut organisms introduced into the bloodstream. Although hypovolemic shock should always be strongly considered in trauma and/or surgical cases, this patient's bleeding appears to have been controlled upon arrival/in the operating room, and there was no overt source of bleeding or fluid loss post-operatively. Furthermore, being in a monitored setting, the patient was likely receiving fluids and/or transfusions.

The patient's presentation is also less consistent with cardiogenic shock, as the patient has no cardiac history, his ECG is normal, and cardiogenic shock is unlikely to cause DIC. Anaphylactic shock is unlikely, as there is no suspected allergen, and the patient is not known for any allergies. Neurogenic shock is also unlikely, given the unremarkable neurological examination and lack of evidence of head or spinal cord injury, although it can be a cause of DIC. Case adapted from Kaplan Medical (1).

3 | INITIAL APPROACH

Shock is a life-threatening pathophysiologic state referring to inadequate organ perfusion, which can progress to end-organ dysfunction and eventually, multiple organ failure and death (2, 3). Shock may arise from increased oxygen demands, impaired delivery of oxygen, impaired utilization of oxygen, or a combination of these processes (3).

There are many different etiologies of shock, which can be broadly classified into four types of shock: hypovolemic shock (i.e., secondary to massive blood and/or fluid loss); cardiogenic shock (i.e., impaired cardiac pump function, arrhythmias, or structural defect); obstructive shock (i.e., impaired cardiac output due to obstruction); and distributive shock (i.e., pathologic vasodilatation resulting in redistribution of body fluids out of the vasculature, which can be further divided into septic, anaphylactic, and neurogenic shock) (2, 3).

The diagnosis of shock is clinical, frequently manifested by hypotension and tachycardia, as well as the findings specific to the type of shock. While some patients present with a readily identifiable etiology of shock (e.g., bleeding after trauma), other cases of shock present undifferentiated. Nevertheless, early recognition and empiric treatment are key, as shock is associated with a very high mortality rate (2, 3).

3.1 | General Overview

The initial approach to shock is generally comprised of a primary survey (rapid assessment of the airway, breathing, and circulation), followed by a focused history and physical examination. A means to monitor vital signs (telemetry, blood pressure, pulse oximetry) and intravenous access with large-bore IVs should be established early on. The suspected etiology and differential diagnosis then guide further diagnostic testing; however, there is no isolated test that is specific or sensitive for shock. Studies should also be performed to determine the presence of end-organ dysfunction, which may also serve to assess response to therapy. Management of shock entails circulatory support and treatment of the underlying cause (2, 3). The individual components of the approach include (but are not limited to) the following:

3.2 | History

Comprehensive history-taking may be difficult to conduct in cases of shock; obtaining collateral history may therefore be warranted. Patients may voice nonspecific complaints, such as lethargy and weakness; they may also respond inappropriately if they are presenting with altered mental status, a manifestation of cerebral hypoperfusion (2, 3).

Taking a history may reveal important symptoms and/or events that give insight into the development of shock. Trauma, melena, hematemesis, and vagi-

nal bleeding are suggestive of hypovolemic shock secondary to hemorrhage; diarrhea, vomiting, and high ostomy output could indicate non-hemorrhagic hypovolemic shock. Cardiogenic shock or obstructive shock may be preceded symptomatically by chest pain, palpitations, shortness of breath, lower extremity swelling, or syncope. Anaphylactic shock may present with the sudden onset of skin rash, swelling, and shortness of breath following exposure to a known trigger. Septic shock may be associated with infectious symptoms: fever, chills, respiratory symptoms, dysuria, or abdominal/flank pain (2, 3).

3.3 | Heart Rate

The heart rate (HR) may be elevated (>100 beats/minute) as a compensatory mechanism to maintain vital organ perfusion in cases of hypotension. However, patients with neurogenic shock may present with bradycardia due to decreased sympathetic tone (2). In older adults, a blunted tachycardic response may occur due to myocardium that is stiffened and less sensitive to catecholamines; a threshold HR of 90 may therefore define tachycardia in this population (4).

3.4 | Blood Pressure

Hypotension is defined by a systolic blood pressure (BP) <90mm Hg and/or diastolic BP <60 mm Hg. Although it is commonly associated with states of shock, hypotension and tachycardia may not be present in the early stages (3, 5). A mean arterial pressure (MAP) of 60-65mm Hg is generally recognized as the minimum pressure for adequate organ perfusion (5). In adults above the age of 65, a systolic BP of less than 110mm Hg is correlated with increased mortality and considered a better benchmark to account for declining physiologic capacity, especially in the setting of trauma (4, 6).

3.5 | Physical Examination

The jugular venous pressure (JVP), which reflects the patient's fluid status and cardiac function, should be assessed visually (2, 3, 7). Signs of an elevated JVP (jugular venous distension, Kussmaul sign, hepatojugular reflex) can suggest cardiogenic and obstructive causes of shock. Murmurs, arrhythmias, and dependent edema may also accompany cardiogenic shock (2, 3). Tachypnea is frequently present, which can be related to lactic acidosis (in the context of anaerobic metabolism) or the primary insult (e.g., pulmonary embolism, pneumonia, pneumothorax, heart failure, etc.) (2, 3). The extremities may be cool to touch with thready pulses and a slow capillary refill, reflecting vasoconstriction and hypoperfusion. Conversely, the skin may be warm if there is abnormal dilatation in the early stages of distributive shock (3). It is also important to identify potential sources of hemorrhage or fluid loss. A rectal examination may be indicated to rule out melena or hematochezia. Skin integrity should be verified should there be suspicion of a burn injury (2, 3).

3.6 | Hemodynamic Parameters

Hemodynamic parameters underlining cardiac physiology (Figure 1) may be used to characterize shock (2, 3). Preload, referring to the extent of stretch of the heart muscle fibres before the onset of systole, increases with venous constriction and increased circulating blood volume. Preload is therefore decreased with hypovolemic and distributive shock; however, it may be increased in cases of cardiogenic and obstructive shock (2, 8). Cardiac output (CO) is a measure of the blood volume (in litres) ejected from the heart in one minute. It is dependent on the stroke volume (SV) and HR. CO is increased in septic and anaphylactic shock (to maintain blood pressure), but decreased in cardiogenic, obstructive, hypovolemic, and neurogenic shock (2, 8). Systemic vascular resistance (SVR) and afterload are increased in all forms of shock except distributive shock, where there is pathologic vasodilatation (2, 3).

Mixed venous oxygen saturation (SvO_2) denotes the percentage of oxygen bound to hemoglobin sampled from the right heart (i.e., the oxygen saturation of the blood from the superior and inferior vena cava as well as the coronary sinus), reflecting the body's total oxy-

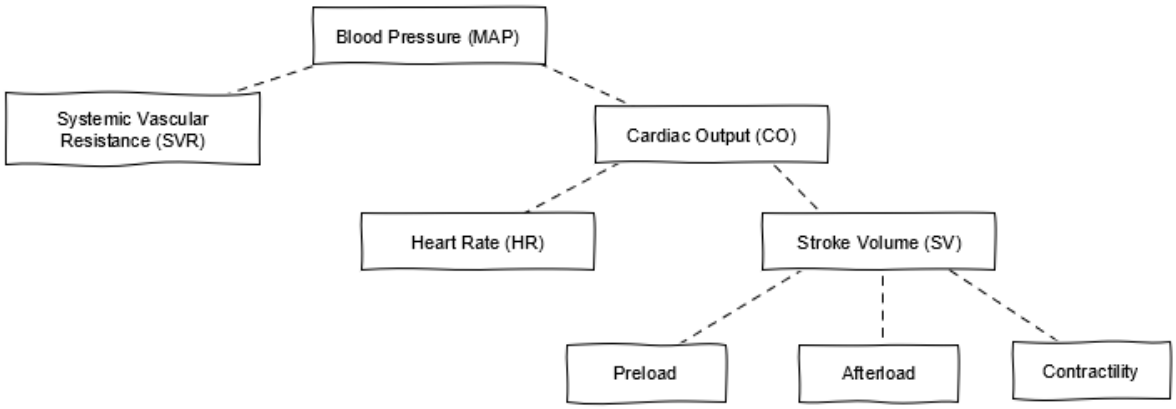

FIGURE 1 Cardiac Physiology.
A figure of the parameters constituting blood pressure that allows for organ perfusion, adapted from "Cardiac physiology" by Amboss. (8)

gen consumption (2). The reference range is 65-70% (9). A decreased SvO_2 reflects increased oxygen needs (e.g., due to fever, exercise, or seizures), or increased tissue extraction due to decreased oxygen delivery or availability (9). SvO_2 is decreased in hypovolemic, cardiogenic, obstructive, and neurogenic shock, but may be increased in septic and anaphylactic shock (2). In the latter cases, it is proposed that high SvO_2 reflecting low oxygen consumption at the tissue level may be associated with mitochondrial and microvascular dysfunction (10).

3.7 | Additional Assays

Bedside Ultrasonography: (i.e., FAST examination) can narrow the differential diagnosis of shock by ruling in/out: intra-peritoneal free fluid/hemorrhage, abdominal aortic aneurysm, pneumothorax, hemothorax, cardiac tamponade, as well as assessing global cardiac function and intravascular status (3, 11).

Arterial Blood Gas Analysis: Lactic acidosis is the result of elevated serum lactate from the anaerobic metabolism in underperfused organs. The acidosis can lead to altered mental status as well as tachypnea (2).

Clotting Parameters: DIC, characterized by thrombosis, hemorrhage, and consumption of platelets and clotting factors caused by systemic activation of the clotting cascade, can develop in cases of trauma, shock, and sepsis due to their associated proinflammatory states. Typical findings include thrombocytopenia, prolonged PT and PTT, decreased fibrinogen levels, and elevated levels of fibrinogen degradation products (e.g., D-dimer) (2, 12).

Liver/Renal Function Tests: Increased urea and creatinine suggest acute renal failure as a result of kidney hypoperfusion; similarly, hyperbilirubinemia and elevated AST/ALT can indicate acute liver failure (2).

Urine Output: The patient may become oliguric, another sign of acute renal failure. This can be measured by placing a urine catheter in the bladder (2).

4 | BEYOND INITIAL APPROACH

Table 1 summarizes the various presentations of shock, categorized by type and possible underlying etiologies, as well as their associated findings and potential treatment options.

4.1 | Intravenous Fluids

Intravenous fluids are first-line agents in the management of shock to increase BP and consequently, improve organ perfusion. They are generally administered until there is an adequate BP and perfusion response, until there is evidence of harm (e.g., pulmonary edema and intra-abdominal hypertension), or when the antici-

pated hemodynamic response is not achieved, warranting further hemodynamic support (e.g., vasopressors).

The total volume in fluid resuscitation varies; while septic shock and hemorrhagic shock can require volumes (sometimes upward) of 2 to 5L, obstructive shock and cardiogenic shock may necessitate relatively smaller volumes, up to 1L. Although there is no one ideal choice of fluid, commonly used fluids include crystalloids (e.g., Ringer's lactate and normal saline), as well as blood products in the setting of hemorrhagic shock (13).

4.2 | Pressors in the Intensive Care Unit

Vasopressors and inotropes are an additional form of hemodynamic support used in the management of shock. They are medications that are administered intravenously, often in a continuous infusion to allow for immediate titration. Vasopressors increase vasoconstriction, resulting in increased SVR; inotropes increase cardiac contractility, which increases CO. SVR and CO in turn comprise MAP (Figure 1). A MAP of 60-65mm Hg is recognized as a reasonable target for adequate organ perfusion (5).

The most common catecholamines are phenylephrine, norepinephrine, and epinephrine, which have varying effects on alpha- and beta-adrenergic receptors. Alpha receptors induce peripheral vasoconstriction that increases SVR; beta-1 receptors have chronotropic and inotropic effects on the heart, to increase HR and contractility, respectively. Phenylephrine is a pure alpha-1 agonist that increases SVR and BP; however, it can cause reflex bradycardia. Norepinephrine and epinephrine both have alpha-1 and beta activity (to different degrees), and so they increase SVR, HR, CO, and BP (5).

Vasopressin is a peptide hormone that acts on V-1 and V-2 receptors to contract the smooth muscle of vessel walls and to increase reabsorption of water by the kidneys, respectively; this increases SVR and BP (5, 14). Dopamine is a precursor of norepinephrine and epinephrine that alters renal blood flow, SVR, HR, contractility, and CO. It acts on dopaminergic receptors as well as alpha- and beta-adrenergic receptors, and its effects vary in a dose-dependent fashion (5). Dobutamine, primarily acting on beta-1 receptors, increases contractility and CO with minimal effects on BP (5). Milrinone is a phosphodiesterase inhibitor that increases levels of cyclic AMP, resulting in cardiac stimulation (increasing CO) and vasodilatation of peripheral vessels (decreasing BP) (5).

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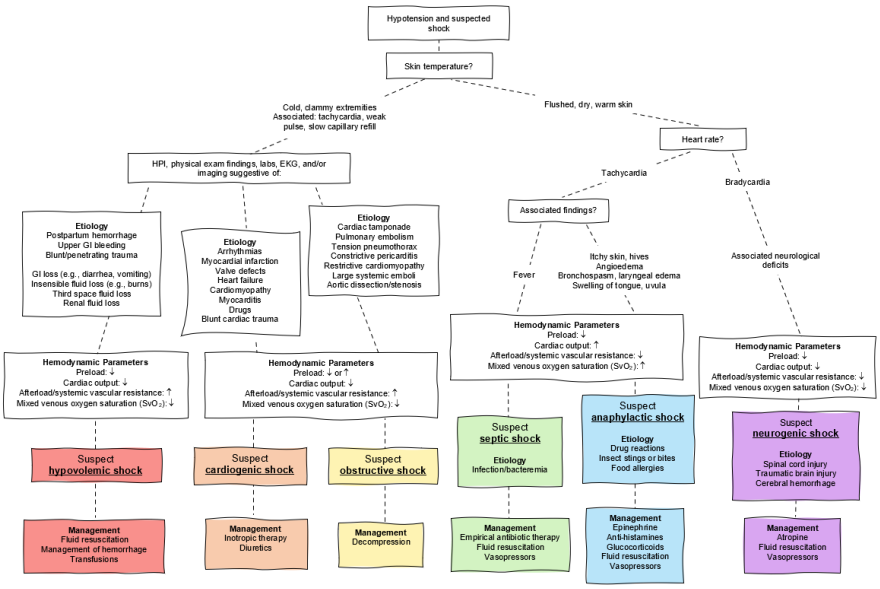
5 | FLOWCHARTS AND TABLES



FLOWCHART 1 Approach to Shock.

A visual flow chart to depict the approach to integrating clinical findings and investigations in suspected cases of shock, adapted from "Overview of the most common types of shock" by Amboss. (2) The initial approach to shock is generally comprised of a primary survey (rapid assessment of the airway, breathing, and circulation), followed by a focused history and physical examination. The suspected etiology and differential diagnosis then guide further diagnostic testing; however, there is no isolated test that is specific or sensitive for shock. Studies should also be performed to determine the presence of end-organ dysfunction, which may also serve to assess response to therapy. Management of shock entails circulatory support and treatment of the underlying cause. (2, 3)

Type of Shock	Hypovolemic Shock	Cardiogenic Shock	Obstructive Shock	Distributive Shock		
				Septic Shock	Anaphylactic Shock	Neurogenic Shock
Etiology	Hemorrhagic: - Post-partum - Ruptured ectopic pregnancy - GI bleed - Trauma Non-hemorrhagic fluid loss: - Vomiting - Diarrhea - High ostomy output - Increased insensible fluid loss (e.g., burns) - Third space fluid loss - Renal fluid loss	Arrhythmogenic Cardiomyopathic: - Myocardial infarction - Heart failure - Cardiomyopathy - Myocarditis Cardiotoxicity: - Drugs Structural: - Valve defects - Septal wall defects - Blunt cardiac trauma	Pulmonary vascular: - Pulmonary embolism - Venous air embolism Mechanical: - Cardiac tamponade - Tension pneumothorax - Constrictive pericarditis - Restrictive cardiomyopathy - Aortic dissection/stenosis	- Infection (pneumonia, pyelonephritis, etc.)	- Drug reactions - Insect stings or bites - Food allergies	- Spinal cord injury - Traumatic brain injury - Cerebral hemorrhage
Pathophysiology	Decreased circulating (intravascular) volume resulting in decreased preload, SV, and CO; secondary to massive blood and/or fluid loss	Decreased CO secondary to impaired pump function of the heart to generate adequate BP	Impaired CO due to obstruction (pulmonary vascular or mechanical)	Pathologic vasodilatation leading to redistribution of body fluids out of the vasculature and relative intravascular volume depletion		
Clinical Findings	Hypotension Tachycardia Thready pulse Cold, clammy extremities Slow capillary refill Findings associated with underlying etiology			- Flushed, dry, warm skin - Tachycardia - Hypotension - Fever - Findings associated with infectious source	- Flushed, dry, warm skin - Tachycardia - Hypotension - Itchy skin, hives - Bronchospasm - Laryngeal edema - Swelling of tongue/uvula - Angioedema	- Flushed, dry, warm skin - Bradycardia - Hypotension - Neurological deficits
Hemodynamic Parameters	Preload: ↓ CO: ↓ SVR: ↑ SvO_2: ↓	Preload: ↑ or ↓ CO: ↓ SVR: ↑ SvO_2: ↓		Preload: ↓ CO: ↑ SVR: ↓ SvO_2: ↑		Preload: ↓ CO: ↓ SVR: ↓ SvO_2: ↓
Extra Diagnostic Tests	- Type and screen	- Cardiac enzymes - Echocardiogram	- CT (PE) - Echocardiogram	- Cultures - CSF studies		
(Potential) Treatment	- Blood products - Fluid resuscitation - Source control	- Inotropic therapy - Diuretics - Cardioversion - Cardiac pacing - Angiography - Cardiac surgery - Intra-aortic balloon pump - Extracorporeal membrane oxygenation	- Systemic thrombolysis - Pericardiocentesis - Pleural decompression	- Infection source control - Broad-spectrum empirical antibiotic therapy - Vasopressors - Fluid resuscitation	- Intramuscular epinephrine - Antihistamines - Glucocorticoids - Vasopressors - Fluid resuscitation	- Atropine - Vasopressors - Fluid resuscitation

TABLE 1 A table summarizing shock, adapted from Amboss' "Overview of the most common types of shock" and Sanderfur's "Approach to Shock". (2, 3)

The diagnosis of shock is clinical, necessitating good understanding of possible underlying etiologies, pathophysiology, as well as the clinical, biochemical, and hemodynamic manifestations of the various presentations of shock. (2, 3)

APPROACH TO
McGill Journal of Medicine

Acute Kidney Injury

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ABSTRACT

Acute kidney injury is defined as an abrupt decline in kidney function, which manifests as an increase in serum creatinine level or a decrease in urine output within a short period of time. It is a commonly encountered entity in the clinical setting and necessitates a systematic diagnostic approach. Acute kidney injury etiologies are classified as either prerenal, intrinsic renal, or postrenal. This article presents the key elements of history taking, physical examination, and laboratory investigations when assessing a patient for acute kidney injury to properly classify its etiology. The use of imaging modalities is also discussed. Common etiologies of acute kidney injury in each category are highlighted. Lastly, this article provides a brief overview of management principles for acute kidney injury with a particular emphasis on indications for initiation of dialysis.

KEYWORDS

Acute kidney injury, Acute tubular necrosis, Creatinine, Renal failure, Urine microscopy.

1 | QUESTION

A 39-year-old female presents to the emergency department at the request of her family physician due to a 2-day history of vomiting and profuse diarrhea. She returned from a cruise yesterday and recalls other travelers were sick on the cruise. She is known for anxiety, gastroesophageal reflux, and patellofemoral syndrome. Her prescribed medications are sertraline and ranitidine. On history, she reports feeling well until two days ago. Since then, she has been vomiting and having diarrhea incessantly. She also had very little appetite and has not been eating or drinking well. She has been mostly staying in bed and reports some dizziness when standing up to go to the bathroom. She saw her family doctor yesterday, who obtained blood tests. Notably, her creatinine level was 135 μmol/L. Three months ago, her creatinine level was 67 μmol/L on routine blood work.

Which of the following physical examination findings is not consistent with your suspected cause of acute kidney injury?

A. Absence of crackles on lung exam
B. Orthostatic hypotension
C. Distended bladder
D. Low jugular venous pressure
E. Postural tachycardia

2 | ANSWER

C. This patient's history is suggestive of a prerenal acute kidney injury in the context of significant dehydration. Indications of this etiology include poor oral intake and significant fluid loss from vomiting and diarrhea. The patient also complains of dizziness upon standing, which reflects orthostatic hypotension secondary to hypovolemia. On physical examination, she would be expected to have findings consistent with hypovolemia, which include absence of crackles on lung exam (A), orthostatic hypotension (B), low jugular venous pressure (D), and postural tachycardia (E). A distended bladder is more consistent with postrenal acute kidney injury, which is commonly due to benign prostatic hyperplasia in older men. It is not a finding that would be associated with prerenal acute kidney injury.

3 | INITIAL APPROACH

3.1 | Diagnosis

Acute kidney injury (AKI) is defined as any of the following: **1.** Increase in serum creatinine $\geq$26.5 μmol/L within 48 hours; or **2.** Increase in serum creatinine $\geq$1.5 times the baseline, which is known or presumed to have occurred within the prior 7 days; or **3.** Urine volume $<$0.5 mL/kg/h for 6 hours (1). It is important to distinguish between AKI and chronic kidney disease (CKD). Hence, a recent creatinine level indicating the patient's baseline is especially useful. When it is not available, CKD is suspected based on certain laboratory findings (e.g., normocytic anemia, elevated parathyroid hormone) and radiologic findings (e.g., small, shrunken kidneys with cortical thinning). AKI on CKD is also very common. Therefore, measuring the serum creatinine over several days may be needed to document an AKI (2).

3.2 | History Taking

The patient's history often provides important clues regarding the cause of AKI: prerenal, postrenal, or intrinsic.

Prerenal AKI results from poor renal perfusion. It is often associated with an absolute volume loss, which can be suggested by a history of poor fluid intake or fluid loss such as vomiting or diarrhea (2). An improvement of the AKI after fluid resuscitation is indicative of this cause for the prerenal AKI (3). Certain medical conditions such as congestive heart failure, cirrhosis, and sepsis can also result in poor renal perfusion resulting in prerenal AKI. Lastly, specific medications are associated with prerenal AKI due to their effect on the afferent and efferent arterioles. These include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (4).

Postrenal AKI results from the obstruction of the urinary flow anywhere from the kidney to the urethra. When the obstruction is above the bladder, it usually must affect both kidneys to result in significant AKI. The patient may complain about difficulty voiding and poor urine output (1). Benign prostatic hyperplasia is a common cause in older men (2).

Intrinsic renal AKI is due to a pathologic process within the kidneys. It has a vast differential diagnosis. If there is no clear history of prerenal or postrenal AKI, intrinsic etiologies must be suspected. A thorough review of the patient's past medical history, medications, and exposure to potential nephrotoxins is essential.

Risk factors for AKI could also be elicited on history taking. These include CKD, diabetes mellitus, older age, chronic liver disease, congestive heart failure, and renal artery stenosis (3).

3.3 | Physical Examination

An assessment of the patient's volume status is important in the evaluation of AKI. It is especially useful if a prerenal etiology is suspected. Prerenal AKI is suggested by signs of hypovolemia: orthostatic hypotension, postural tachycardia, and low jugular venous pressure. Signs of congestive heart failure (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) or cirrhosis (e.g., ascites, telangiectasias, and palmar erythema) also point towards a prerenal etiology. Acute tubular necrosis (ATN) may result after prolonged prerenal AKI and present with similar physical ex-

amination findings (2).

A patient with postrenal AKI with a below bladder obstruction could have bladder distention and suprapubic discomfort on palpation. However, these signs would not be noted for an obstruction at a higher level. Prostate enlargement is appreciated on examination of patients with benign prostatic hyperplasia. Postrenal AKI due to kidney stones is suggested by costovertebral angle tenderness (2).

The physical examination findings for intrinsic causes of AKI are greatly dependent on the etiology. All patients with AKI should have their urine output closely monitored (3).

3.4 | Initial Laboratory Investigations

Blood investigations: A complete blood count and full metabolic profile are ordered in the evaluation of AKI. The serum creatinine is important for the diagnosis of AKI and for monitoring its evolution (4). Some causes of AKI are associated with a characteristic timeline in terms of changes in serum creatinine. For instance, contrast nephropathy usually results in a rise of creatinine within 24-48h, peaks within 3-5 days, and resolves within a week. Moreover, hyperkalemia, hyperphosphatemia, and metabolic acidosis are possible complications of AKI (2).

A complete blood count is also useful in finding the etiology of the AKI. For instance, in a patient with suspected sepsis, an elevation in white blood cells could be present (2).

Urine investigations: Urinary tests are especially useful when trying to distinguish between prerenal AKI and acute tubular necrosis (ATN). In prerenal AKI, the tubular function is preserved and the kidneys increase sodium reabsorption and urinary concentration in response to decreased renal perfusion. However, this function is lost in ATN (5). The findings of both conditions are shown in Table 1.

Urinalysis is part of the initial workup for AKI. It provides information regarding the concentration of the urine. It also detects proteinuria, white blood cells, and red blood cells in the urine. However, urinalysis only detects albumin. Therefore, assessing for the presence of other types of protein requires further testing (2).

Urine electrolytes and osmolality are also often obtained in the evaluation of AKI. A fractional excretion of sodium is calculated with the formula $\frac{100 \times urinary\ sodium \times serum\ creatinine}{serum\ sodium \times urinary\ creatinine}$. The units for urinary and serum creatinine are μmol/L while the units for the other measurements are mmol/L. It is important to note that for patients on diuretics, these values are less reliable (4).

Urine microscopy is particularly useful in the evaluation of AKI to assess for the presence of casts. Prerenal AKI is usually associated with an unremarkable urine microscopy although it occasionally presents with hyaline casts. Urine microscopy in postrenal AKI is usually unremarkable. Urine microscopy is especially helpful when assessing for intrinsic AKI. In ATN, tubular epithelial cell casts and granular (muddy brown) casts are seen. White blood cell casts are suggestive of acute interstitial nephritis. Red blood cell casts are seen in glomerulonephritis or vasculitic conditions. Most vas-

	Prerenal	Acute tubular necrosis
Urine sodium	<20 mmol/L	>40 mmol/L
Fractional excretion of sodium	<1%	>2%
Urine osmolality	>500 mOsm/kg	~300 mOsm/kg
Urine microscopy	Normal or hyaline casts	Renal tubular cell and granular casts (muddy brown)

Adapted from reference 5.

TABLE 1 Findings on urinary tests for prerenal acute kidney injury and acute tubular necrosis.

cular causes of AKI other than vasculitis present with a normal urine microscopy (2).

Imaging: The use of a bladder scan to assess for the postvoid residual is a simple test for postrenal AKI. If the postvoid residual is greater than 200 mL, a below bladder obstruction should be suspected (4).

A renal ultrasound is also often ordered when evaluating for AKI. It is particularly helpful to rule out obstruction as the ultrasound could show hydronephrosis. Imaging studies such as computed tomography can also be used to visualize kidney stones or a neoplasm if they are suspected as the cause of the obstruction (4). Moreover, imaging may help in differentiating AKI and progression of CKD in patients whose baseline creatinine is unclear (3). In CKD, the kidneys usually appear smaller whereas the kidneys are of normal size in a patient with AKI without CKD. However, since CKD is most commonly caused by diabetic nephropathy, kidney sizes of CKD patients could also be normal (3).

Genetic testing: Usually, the above investigations provide a clear etiology for the AKI. However, genetic testing is occasionally used to assess for etiologies of AKI. For instance, atypical hemolytic uremic syndrome is commonly associated with genetic defects in the complement pathway and may lead to AKI. Hence, genetic testing in AKI could affect treatment decisions (3).

4 | BEYOND INITIAL APPROACH

4.1 | Etiologies of AKI

Various etiologies of the prerenal, intrinsic, and postrenal AKI are presented in Table 2. Intrinsic causes of AKI are numerous and are broadly categorized as tubular, interstitial, glomerular, and vascular. A brief description of four common etiologies in each category will be provided below.

Acute tubular necrosis (ATN): The most common cause of intrinsic AKI in hospitalized patients is ATN. The etiology is either ischemic from prolonged poor renal perfusion or nephrotoxic. Compared to prerenal AKI, the ischemic injury has resulted in tubular injury and the AKI does not improve with restoration of blood flow to the kidneys (4). Nephrotoxins are either endogenous or exogenous. For example, rhabdomyolysis and hemolysis both result in endogenous nephrotoxin-associated AKI, in part due to the direct tubular toxicity of myoglobin and hemoglobin respectively. In multiple myeloma, free light chains can also cause direct tubular toxicity (3). Exogenous nephrotoxins include contrast agents used in CT imaging and medications. Antimicrobial agents (e.g., vancomycin, amphotericin B, and acyclovir) and chemotherapy agents (e.g., cisplatin, carboplatin) are common culprits (2).

Acute interstitial nephritis: Acute interstitial nephritis is most commonly a result of medications such as antimicrobial agents, analgesics, proton pump inhibitors, anticonvulsants, and diuretics. However, it could also be associated with infections and systemic diseases, mainly rheumatologic (6). Patients present with fever, arthralgias, and a rash (2).

Glomerulonephritis: Glomerulonephritis (GN) encompasses diseases involving the glomerular podocytes, mesangial, and endothelial cells. They commonly present with red blood cell casts on urine microscopy (2). The laboratory investigations can suggest one particular cause of GN. For instance, elevated antineutrophil cytoplasmic antibody (ANCA) is associated with ANCA vasculitis. In another example, anti-glomerular basement membrane (anti-GBM) antibody is suggestive of anti-GBM disease. Also, low complement levels are seen in lupus nephritis, membranoproliferative GN, and postinfectious GN. Lastly, elevated antistreptolysin O titer is usually indicative of poststreptococcal GN. A kidney biopsy is often done if GN is suspected (4).

Hemolytic uremic syndrome: This condition usually follows a recent diarrheal episode and presents with the triad of AKI, thrombocytopenia, and microangiopathic hemolytic anemia (7). It is often due to the Shiga toxin released by bacteria such as *Escherichia coli*. Clues in laboratory investigations include anemia, thrombocytopenia, elevation in LDH, and presence of schistocytes on blood smear (2).

4.2 | Management of AKI

General principles: Management of AKI is directed at reversing the underlying cause. Moreover, supportive care is provided concerning fluid, electrolyte, and acid-base balance. It is also important to review the patient's medications to discontinue nephrotoxic agents. Some medications' dosing needs to be adjusted depending on the level of kidney function of the patient (3).

Correcting the underlying etiology: Prerenal AKI and ATN are often due to hypovolemia. Hence, the management includes the use of intravenous fluids. Isotonic fluids such as normal saline and Ringer's lactate are usually chosen. Aggressive fluid resuscitation is also central to the treatment of AKI as a result of sepsis and anaphylaxis. Moreover, vasopressors are sometimes indicated to help maintain adequate perfusion. If AKI is secondary to congestive heart failure, cardiac function should be optimized (3).

The treatment of postrenal AKI depends on the site of the obstruction. As the most common etiology is benign prostatic hyperplasia, management of this condition with alpha blockers and 5-alpha reductase inhibitors improves the AKI. Some patients require a catheter to relieve the obstruction. The involvement of urology is usually encouraged in managing patients with postrenal AKI (3).

The management of intrinsic AKI is entirely dependent on the etiology. This is usually complex and above the scope of what a medical student is expected to know.

Supportive care: AKI can be complicated by various metabolic abnormalities. Metabolic acidosis is corrected with oral or intravenous infusion of sodium bicarbonate. Hyperkalemia also often occurs in patients with AKI. If there is presence of characteristic electrocardiogram changes, calcium gluconate must be administered immediately to stabilize cardiomyocyte membranes. Moreover, agents to shift potassium intracellularly (e.g., insulin, beta-agonists) and agents to increase elimination

Prerenal acute kidney injury	
Intravascular volume depletion	Vomiting, diarrhea, poor oral intake, hemorrhage, diuretic overuse
Systemic vasodilation	Sepsis, anaphylaxis, cirrhosis
Intrarenal vasoconstriction/dilation	Congestive heart failure, cirrhosis, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (dilation of efferent arteriole resulting in lower intraglomerular pressure), nonsteroidal anti-inflammatory drugs (constriction of afferent arteriole)
Intrinsic acute kidney injury	
Glomerular	Post-infectious glomerulonephritis, anti-glomerular basement membrane disease, membranoproliferative glomerulonephritis, lupus nephritis, IgA glomerulonephritis, vasculitis
Interstitial	Acute interstitial nephritis
Tubular	Acute tubular necrosis
Vascular	Vascular, malignant hypertension, renal atherosclerotic emboli, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, scleroderma renal crisis, renal vein thrombosis
Postrenal acute kidney injury	
Extrarenal obstruction	Benign prostatic hyperplasia, blocked catheter, malignancy, retroperitoneal fibrosis
Intrarenal obstruction	Nephrolithiasis, blood clots, malignancy

Adapted from references 1 and 4.

TABLE 2 Etiologies of prerenal, intrinsic, and postrenal acute kidney injury.

of potassium such as ion exchange resins may be used. Lastly, fluid overload is corrected with the use of diuretics (3).

Indications for initiation of hemodialysis: Some patients with AKI will require renal replacement therapy such as hemodialysis. The indications to initiate renal replacement therapy are metabolic acidosis, hyperkalemia, and volume overload refractory to medical management. Moreover, evidence of uremic pericarditis or encephalopathy is also an indication to start renal replacement therapy (4).

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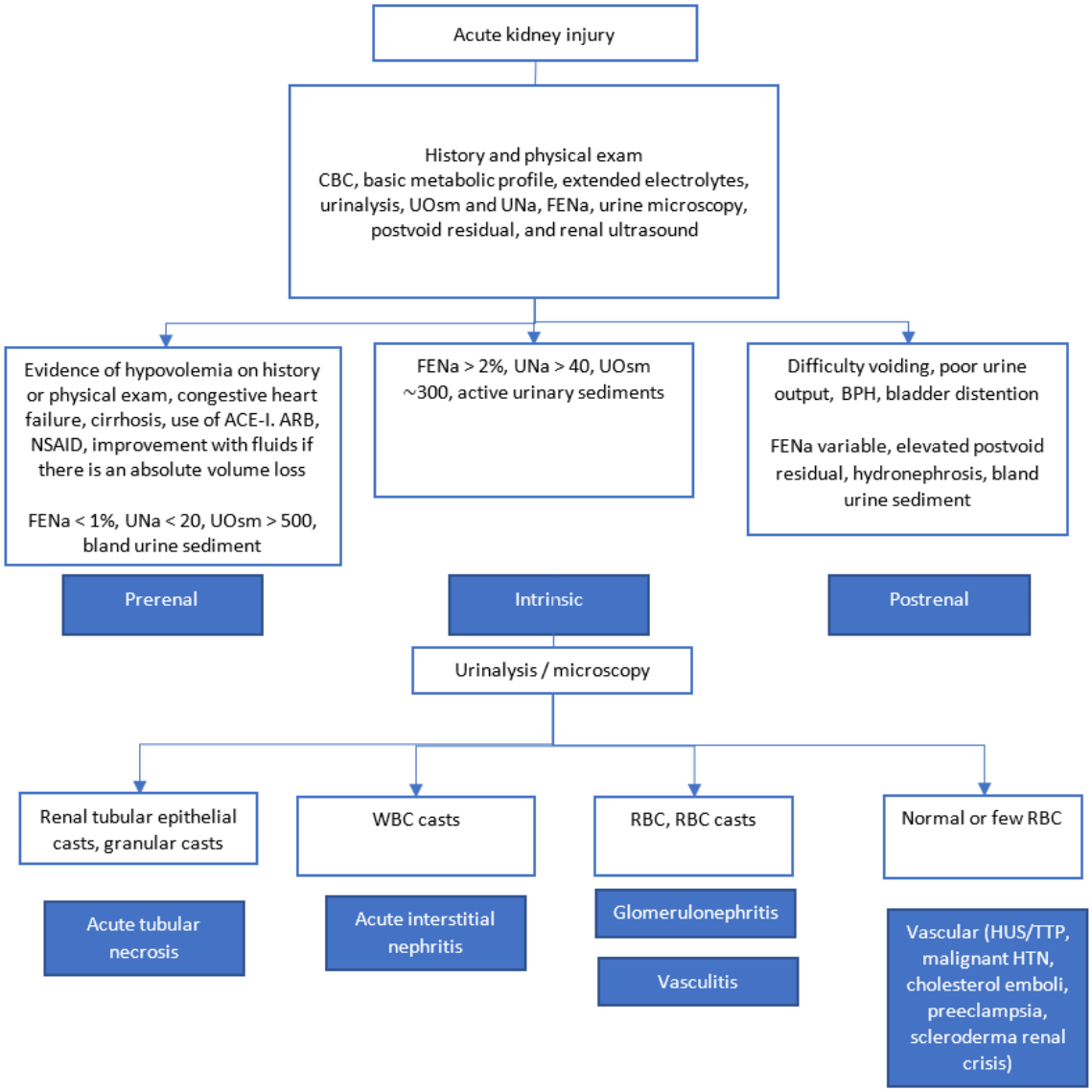
5 | FLOWCHARTS



FLOWCHART 1 Approach to acute kidney injury: Basic algorithm to determine the appropriate investigations and differential diagnoses of acute kidney injury.

CBC = Complete blood count; UOsm = Urinary osmolality (mOsm/kg); UNa = Urinary sodium concentration (mmol/L); FENa = Fractional excretion of sodium; RBC = Red blood cell; WBC = White blood cell; HUS = Hemolytic uremic syndrome; TTP = Thrombotic thrombocytopenic purpura; HTN = Hypertension; ACE-I = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; NSAID = Nonsteroidal anti-inflammatory drugs; BPH = Benign prostatic hyperplasia. Adapted from references 2, 4, and 8.

APPROACH TO
McGill Journal of Medicine

Strabismus

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ABSTRACT

Strabismus is characterized by a misalignment of the eyes. It is commonly referred to as crossed eyes or lazy eyes. A thorough physical examination and review of family history should be performed by clinicians when strabismus is suspected. The Hirschberg corneal reflex test, cover test, cover-uncover test, and alternate prism cover tests are commonly used to identify and diagnose strabismus. Strabismus requires a referral to an ophthalmologist. Treatment of strabismus may involve eye patches, cycloplegic drops, prescription glasses, and surgery. Strabismus can result in vision loss due to amblyopia, double vision, psychosocial concerns, and/or impaired depth perception.

KEYWORDS

Estropia, Strabismus, Cover test, Cover-uncover test, Corneal light reflex, Ophthalmology

1 | CASE/QUESTION

A 6-month-old girl is seen for her well-baby visit and is noted to have a "lazy" left eye. She has a normal birth history and there is no family history of ocular concerns. She meets all of her developmental milestones and is feeding well. Her parents say that her eyes have been like this since birth. On physical exam, the clinician noted that the left eye appears to be turned inwards. The Hirschberg corneal light reflex is notable for mild deflection of the light on the left eye temporal to the pupil. She is able to track toys and other objects well. Pupils are round, equal, and reactive to light and there is a normal red reflex in both eyes. No relative afferent pupillary defect is present. When the right eye is covered, the left eye moves outward to fixate. When the right eye is uncovered, the left eye turns in again. When the left eye is covered, the right eye is straight and fixating normally. When the left eye is uncovered, the right eye remains straight, but the left eye remains

inwardly deviated. After dilating the pupils with eye drops, the clinician measures refractive errors on the right and left eye of +0.50 and +1.00, respectively. Physical examination is otherwise unremarkable.

What is the next best step?

(a) Patch the right eye
(b) MRI of the brain and orbits
(c) Patch the left eye
(d) Strabismus surgery to straighten the eyes
(e) Prescribe glasses for refractive error

2 | ANSWER

A, Strabismus can result in vision loss due to amblyopia. To allow for correction, the strong eye should be covered with a patch to allow the amblyopic "lazy" eye to return to normal function. It is also important to check for refractive error, which may help to treat both strabismus and amblyopia in certain circumstances. Strabismus surgery in this case may be indicated, but the most important first step is to start treating the amblyopia.

3 | INITIAL APPROACH

Strabismus is defined as an ocular misalignment. (1) It is classified by the alignment of the eyes relative to each other and can be either horizontal or vertical. The two forms of strabismus are tropia (manifest deviation, or present when an individual views a target with both eyes open) and phoria (latent deviation, or present only when one eye is occluded). Manifest deviations can be diagnosed with the cover test and latent deviations can be diagnosed with a cover/uncover or alternate prism cover test. This approach is summarized in Figure 1. Figures 2 and 3 demonstrate an exotropia and hypertropia, respectively.

Deviations can be further classified as constant or intermittent. A constant deviation is always present while an intermittent deviation is only present in specific situations, such as when the patient is fatigued or ill. In addition, deviations can be classified as comitant and incomitant. Comitant deviations are the same degree in all positions of gaze while incomitant deviations are more pronounced in certain positions of gaze. Comitant deviations are more common and usually benign, while incomitant deviations are uncommon and frequently a sign of serious underlying pathology. Comitant and incomitant deviations are demonstrated in Figures 4 and 5, respectively.

To summarize with an example, a patient presents with a horizontal deviation with their left eye always turning inward and not changing with the position of gaze. On examination, they have a positive cover/uncover test. This would be classified as a left constant, comitant, esotropia. Of note, esotropia is the most common form of strabismus. (2)

4 | BEYOND INITIAL APPROACH

To better understand strabismus, we present the relevant anatomy, etiology, important components of history-taking, physical examination, special tests, and available treatments.

Strabismus is the result of ocular misalignment, so it is important to be familiar with the function of the 6 extraocular muscles that control eye movement and their innervation. The extraocular muscles are innervated by three cranial nerves (CN). CN VI (abducens nerve) controls the lateral rectus muscle which moves the eye laterally. A CN VI palsy typically presents with an incomitant esotropia and should raise suspicion for elevated intracranial pressure. CN IV (trochlear nerve) controls the superior oblique muscle which internally rotates the move and moves it downward when the eye is looking inward. A CN IV palsy presents with a head tilt away from the side of the palsy. CN III (oculomotor nerve) controls the remaining muscles of eye movement (superior rectus, inferior rectus, medial rectus, and inferior oblique). In addition, CN III is involved in elevation of the eyelid via innervation of the levator palpebrae superioris muscle and constriction of the pupil via parasympathetic innervation of the sphincter pupillae. CN III palsy

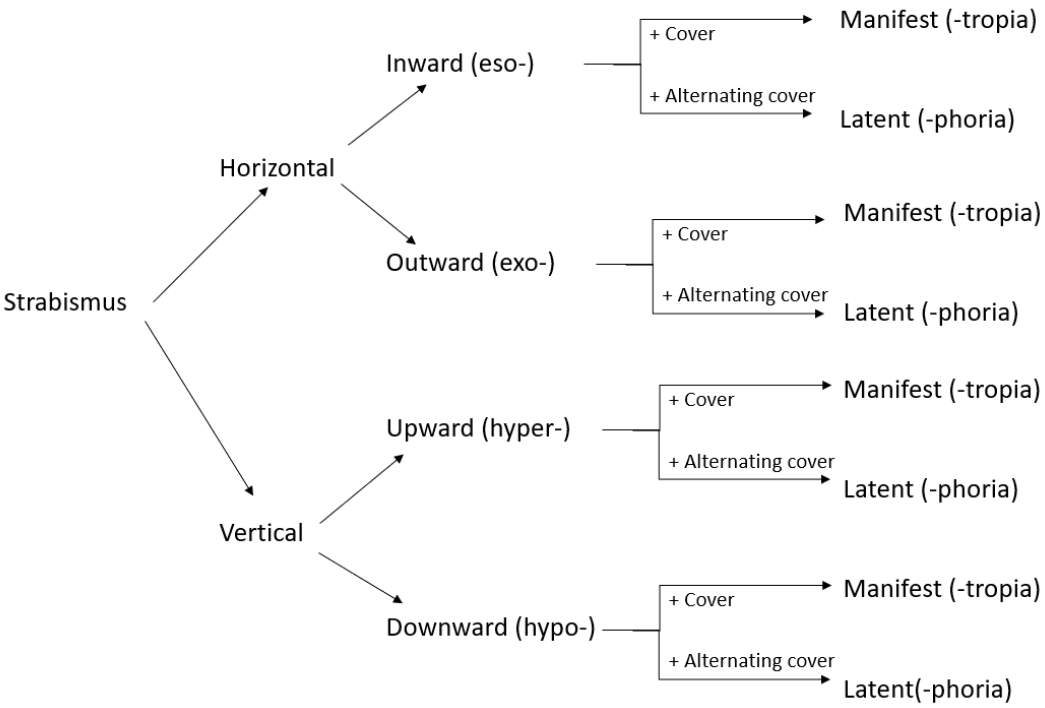

FIGURE 1 An Approach to Strabismus

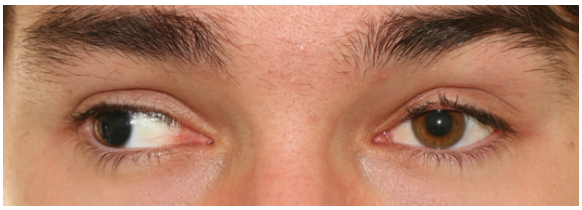

FIGURE 2 Exotropia of the right eye confirmed with a nasal corneal light reflex (Hirschberg Test).

presents as a "down and out" eye with a fixed, dilated pupil, and ptosis. (3) Detailed diagrams regarding the anatomy of the orbit, extra-ocular muscles, and cranial nerves are available in orbital anatomy textbooks. (4)

Strabismus is most frequently diagnosed in children and can lead to amblyopia, which is permanent reduced visual acuity in a one eye due to abnormal visual development early in life. Strabismus in adults usually causes diplopia. Normally, the eyes work together to produce similar images that are combined by the visual cortex to allow for depth perception and three-dimensional vision. In children with strabismus, the images from the eyes are too disparate for the brain to combine into a single image. Over time, the brain will suppress (i.e., learns to ignore) one of the eyes which may lead to amblyopia. This will potentially cause a permanent loss of vision in the suppressed eye and a failure of binocular vision to develop normally. Adults rarely develop amblyopia because the visual cortex has already developed. An ocular misalignment can also have a significant impact on psychological development which can lead to deficiencies later in life in terms of social development and maturity. (5) Children with untreated strabismus are more likely to live in areas of lower socioeconomic status and have a low quality of life. (6) Increased screening and education has resulted in a lower global prevalence of ambly-

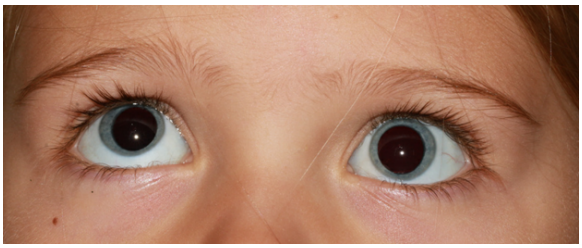

FIGURE 3 Hypertropia of the right eye.

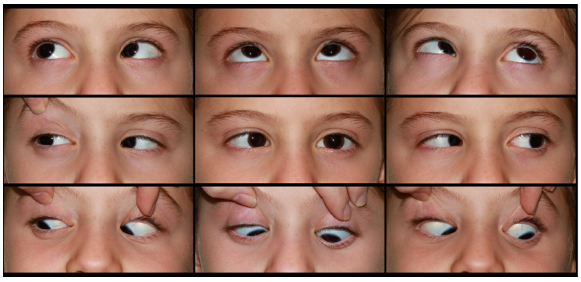

FIGURE 4 Comitant esotropia of the right eye.

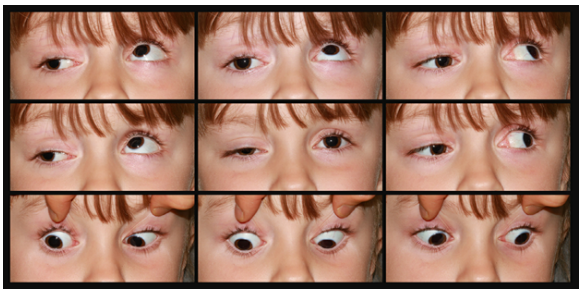

FIGURE 5 Incomitant left hypertropia with elevation deficit of the right eye

opia secondary to strabismus, yet it remains a significant cause of vision loss in children, particularly in immigrant and lower socioeconomic communities due to reduced access to healthcare. (7)

A specific cause of strabismus is not determined in many cases. Strabismus is thought to be multifactorial in nature with contributions from genetic and environmental influences. Both congenital and acquired forms of strabismus exist and it is important to differentiate between the two as an acquired strabismus is a red flag for conditions such as Down Syndrome, cerebral palsy, hydrocephalus, muscular dystrophy, or a cranial mass. (8) There are many risk factors for the development of strabismus. The strongest risk factors for congenital strabismus are anisometropia (Odds Ratio (OR): 7.79), maternal inheritance (OR: 6.42), and critical retinopathy of prematurity (OR: 5.89). (9) Other contributing factors include low birth weight, prematurity, and maternal smoking during pregnancy. (9) The prevalence of congenital strabismus in the general population is estimated to range from roughly 1 to 5%. (10) Acquired strabismus is more common in adults and can result from trauma, surgical procedures, cranial nerve palsies, thyroid dysfunction, and other neurological processes, such as a stroke. The incidence rate of acquired strabismus is roughly 54 cases per 100,000 individuals, or roughly 0.05% of the general population. (11)

For primary care physicians, it is important to con-

duct a comprehensive history and organized physical examination for patients with suspected strabismus. The history must be broad and include risk factors for the development of strabismus. Clinicians should determine if there are any co-morbid conditions, including neuromuscular conditions that can affect eye development and how the brain interprets visual information. A thorough developmental and birth history should be taken as premature/low birth weight is a risk factor for strabismus. It is important for clinicians to note when the strabismus started to determine if it is a congenital or acquired strabismus. It is also essential to characterize whether the strabismus has any triggers and if it is constant or intermittent. As well, the presence of double vision can be an critical clue regarding the presence of strabismus. It should also be clarified whether the child has any other medical or ocular problems. For example, a child who is squinting to focus may have significant refractive error, which is a risk factor and potential cause of strabismus. Lastly, a family history of strabismus should also be explored as this is a major risk factor for developing the condition.

An organized approach should be taken for the physical examination. Any abnormal head posturing including head tilts, turns, and rotations should be noted, as these may indicate accommodative actions taken by the patient to prevent diplopia. Inspection of the eyes should start by observing for position and alignment. Furthermore, the eyelids should be examined for any asymmetry, lid edema, discolorations, or signs of trauma. First, the extraocular movements should be assessed with the six cardinal positions of gaze. During this examination, careful attention should be paid to any restrictions in extraocular motility or any misalignment of the eyes in any position of gaze. Next, visual acuity and colour vision should be assessed with the patient wearing prescription glasses if they have them using age-appropriate options for visual acuity assessment. Lastly, confrontational visual fields and pupils should be assessed for size, symmetry, and reactivity to light.

During the physical examination, in addition to the aforementioned tests, the following specialized tests specifically for strabismus should be employed. The Hirschberg corneal light reflex test assesses for ocular alignment by observing the location of the corneal light reflex relative to the centre of the pupil (Figure 2). To administer this test, the clinician should direct a pen light at the patient and ask them to look directly at it. Individuals with strabismus will have a deviation of the light reflex. In patients with esotropia, exotropia, hypertropia, or hypotropia the cornea light reflex will be displaced temporally, nasally, inferiorly, or superiorly, respectively. The cover test and cover-uncover test should be employed to determine the presence of a manifest deviation or latent deviation, respectively. To perform the cover test, the patient should fixate ahead and cover one of their eyes. A positive cover test occurs when the uncovered eye moves when the contralateral eye is covered. The cover-uncover can be performed by asking the patient to fixate and have them cover the eye. Next, the cover is quickly removed and the examiner notes if there are any movement in the previously covered eye. A positive cover-uncover test occurs when the covered eye moves after removal of the eye cover. Videos of the cover test and the cover-uncover test are available on the American Academy of Ophthalmology website.(12) Lastly, the red reflex should be assessed with direct ophthalmoscopy. Absence of a red reflex can indicate conditions such as retinoblastoma, which should be referred urgently to a pediatric ophthalmologist to perform a dilated fundus examination.

The overall goal of treatment for patients with amblyopia is to improve the vision in the affected eye as much as possible. The primary treatment is with patching of the fellow (dominant) eye. Part-time patching of the fellow eye encourages usage of the amblyopic eye to strengthen and improve vision. Another option includes the usage of dilute cycloplegic drops in the fellow eye, typically atropine. Atropine temporarily impairs accommodation and blurs vision in the stronger eye, particularly at near, forcing the child to use the amblyopic eye to see.

The primary goal of strabismus treatment is to realign the eyes, which can be achieved with different treatments depending on the underlying pathology. In certain types of strabismus, prescription glasses can cor-

rect refractive errors and treat it. Strabismus surgery is often needed for conditions not amenable to refractive correction. Certain types of strabismus are signs of serious underlying pathology and require a workup prior to correction of the misalignment. For instance, an acute-onset CN VI palsy may indicate intracranial disease and needs an urgent workup.

In conclusion, strabismus is an ocular misalignment that can cause vision loss due to amblyopia. It is important to be aware of how to test for strabismus and, in particular, how to identify types of strabismus that are signs of serious underlying pathology. Treatment of amblyopia typically requires covering or blurring the dominant eye, while treatment of strabismus is usually achieved with prescription glasses or surgery.

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APPROACH TO
McGill Journal of Medicine

Hemoptysis

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ABSTRACT

Hemoptysis is the expectoration of blood from the lower airway. A study in the United Kingdom showed that the annual incidence of hemoptysis in primary care is 0.1%. Between 5 and 15% of patients presenting with hemoptysis have a life-threatening hemoptysis.

Approach to hemoptysis can be particularly perplexing for medical students considering the extensive list of differential diagnosis. It is important for physicians to be able to recognize and manage life-threatening hemoptysis as it is associated with high morbidity and mortality if untreated. Understanding when to further investigate patients at risk of lung cancer can help detect the disease at an earlier stage.

This article begins with a brief introduction to life-threatening and nonlife-threatening hemoptysis and provides a detailed discussion of its management including diagnostic approaches followed by appropriate imaging modalities, laboratory findings, and clinical management. The target audience of this article are medical students at their preclinical or clinical phase.

KEYWORDS
Hemoptysis, Diagnosis of hemoptysis, Life-threatening hemoptysis

1 | QUESTION

A 55-year-old woman presents to the clinic with a cough that has produced blood-streaked sputum for the past four days. Associated symptoms include chest pain and subjective fever. She estimated the amount of blood loss to be less than one tablespoon per day. She reports having a previous episode of hemoptysis two months ago, which was diagnosed as bronchitis that resolved after a few days.

She has a previous medical history of hypertension and was recently diagnosed with type 2 diabetes mellitus. She has no known history of rheumatic disease, heart disease, or lung disease. She has a 30 pack-year smoking history and quit smoking 3 years ago. She does not drink alcohol.

Vital signs at the time of presentation were: temperature of 36.7 °C, blood pressure of 132/68mm Hg, heart rate of 74 beats per minute, and oxygen saturation of 98% on room air. Physical examination revealed normal oropharyngeal mucosa with no signs of bleeding or ulceration.

What is the next best next step in the management of this patient?

(A) Chest radiograph
(B) Chest CT scan
(C) Flexible bronchoscopy
(D) Prescribe an antibiotic and send the patient home
(E) Order urinalysis and renal function tests

2 | ANSWER

A) The patient is presenting with less than one tablespoon of blood loss per day, indicating non-life-threatening hemoptysis. Chest-X-ray (CXR) is suggested as a first-line investigation for all patients with hemoptysis. (1) Even if the patient's CXR is normal and the associated symptoms suggest an infectious etiology, the patient should be further evaluated with a computed tomography (CT) scan +/- flexible bronchoscopy. The patient presents with recurrent hemoptysis and lung cancer risk factors (age > 40 and 30 pack-year history of smoking). A study has shown that up to 10% of patients, with risk factors for lung cancer, have normal CXR despite having lung cancer. (2) If the CXR shows an infiltrate, the patient should be treated with antibiotics for pneumonia.

3 | INITIAL APPROACH

The goal of the initial evaluation of hemoptysis includes confirmation of hemoptysis, evaluation of the severity of the bleeding, localization of the origin, and identification of the etiology. (3) The causes of hemoptysis can be divided into five categories: airway diseases, pulmonary parenchymal diseases, pulmonary vascular diseases, bleeding disorders and trauma, and miscellaneous (table 1). (2)

The first step in the initial evaluation of patients with hemoptysis involves **ruling out pseudohemoptysis**. The term hemoptysis refers to expectorated blood originating from the tracheobronchial tree or pulmonary parenchyma. Blood coming from the upper gastrointestinal tract and the upper respiratory tract is called pseudohemoptysis, and can be identified through history and physical examination (Table 2). (4, 5) The second step in the initial evaluation is to **determine whether the hemoptysis is life-threatening** or non-life-threatening.

4 | APPROACH TO LIFE-THREATENING HEMOPTYSIS

4.1 | Definition of Life-Threatening Hemoptysis

Life-threatening hemoptysis (LTH), also referred to as massive hemoptysis, is defined as hemoptysis that causes airway obstruction, abnormal gas exchange, or hemodynamic instability. Hemoptysis is also considered LTH if there is a loss of volume of at least 150 mL over 24 hours or a bleeding rate of $\geq$ 100 mL/hour. (6) Although any etiology causing non-LTH hemoptysis can lead to LTH, the most common causes are bronchiectasis, bronchogenic cancer, tuberculosis, and fungal infections. (6)

The lung is supplied by the pulmonary (carries blood from the right ventricle to the pulmonary capillaries for oxygenation and carbon dioxide excretion) and the bronchial systems (provides arterial blood to the tracheobronchial tree). (7) In 90% of the cases, LTH arises from the high-pressure bronchial circulation. (7, 8)

4.2 | Supportive Care

Patients with true LTH should be admitted to the intensive care unit. The initial management focuses on airway protection, volume resuscitation, and correcting any bleeding disorders. (9) The main risk to consider is asphyxiation. To protect the airway, the patients must be placed into a lateral decubitus position with the affected lung down in order to isolate the non-bleeding lung and protect it from pooling of blood. To further protect the airway, most patients are intubated with a large-bore endotracheal tube, size 8 or above, that can allow the passage of a therapeutic flexible bronchoscope. (6, 8)

Although hemodynamic instability is a rare phenomenon when managing LTH, patients can become

Cause	Etiologies	
Airway disease	• Bronchitis*: Acute or chronic • Bronchiectasis* • Neoplasm*: Bronchogenic carcinoma*, Bronchial carcinoid tumor, Metastatic cancer to bronchus or trachea • Bronchovascular fistula • Dieulafoy disease • Foreign body in airway • Broncholith	
Pulmonary parenchymal disease	**Infection** • Pneumonia* • Tuberculosis* • Lung abscess • Mycetoma* (aspergillosis) and other fungal infections • Parasitic disease	**Rheumatic disease** • Anti-glomerular basement membrane disease (Goodpasture disease) • Granulomatosis with polyangiitis and other vasculitides • Behçet disease • Primary antiphospholipid antibody • Systemic lupus erythematosus **Other** • Genetic defect of collagen • Thoracic endometriosis
Vascular disease	• Pulmonary embolism* • Heart failure* (acquired or congenital), Mitral stenosis • Pulmonary arteriovenous malformation • Pulmonary artery pseudoaneurysm (due to infection, neoplasm, or trauma) • Tracheal-arterial fistulae	• Pulmonary veno-occlusive disease • Pulmonary and bronchial artery aneurysms • Endometriosis
Bleeding disorders trauma	**Bleeding disorders** • Anticoagulant and antiplatelet medications • Disseminated intravascular coagulation (DIC) • Platelet dysfunction (e.g. renal failure) • Thrombocytopenia (ITP, TTP, HUS) • von Willebrand disease	**Trauma** • External blunt or penetrating trauma • Airway stent • Balloon dilation of airway lesion • Biopsy • Bronchoscopy • Endotracheal tube erosion • Transthoracic needle aspiration or biopsy • Pulmonary artery catheter
Miscellaneous	**Drugs and toxins** • Cocaine use, Argemone alkaloid-contaminated cooking oil, Bevacizumab treatment, Nitrogen dioxide toxicity, Hydralazine (hydralazine-induced vasculitis), Riociguat	**E-cigarette or vaping product use associated lung injury (EVALI) Idiopathic/miscellaneous** • Idiopathic pulmonary hemosiderosis • Amyloid • Fibrosing mediastinitis

Most common etiologies; Information from references 2 and 5

TABLE 1 Etiologies of Hemoptysis (Non-Exhaustive List)

Etiology	History findings	Physical examination finding	Confirmatory test / Procedure
Upper gastrointestinal tract	Coffee ground appearance, darker blood, black tarry stools, nausea & vomiting, gastrointestinal disease	Epigastric tenderness, signs of chronic liver disease	Acidic blood, blood mixed with food particles, blood in nasogastric aspiration, esophago-gastro-duedonoscopy
Upper respiratory tract	Bleeding gums, epistaxis, little or no cough or sputum, sore throat	Gingivitis, telangiectasis, ulceration, varices of the tongue, nose, nasopharynx, oropharynx or hypopharynx	Nasopharyngoscopy
True Hemoptysis	History suggestive of bleeding from the lower respiratory tract including cough and sputum secretions; blood may be mixed with sputum	Bleeding not coming from the upper gastrointestinal tract of the upper respiratory tract	CXR; CT scan; Flexible bronchoscopy

Information from references 3 and 4

TABLE 2 Differentiating Features of Pseudohemoptysis

tachycardic and hypotensive, requiring hemodynamic resuscitation (7). In addition, bleeding diathesis in patients with suspected bleeding disorders must be managed.

4.3 | Diagnostic Approach

The optimal diagnostic approach to LTH has not been established. (9) In addition, the sequence of the investigations depends upon the stability of the patient. (9) History, physical examination, and CXR, should be done when possible. (6)

Multiple studies suggest that in the setting of LTH, flexible bronchoscopy is the procedure of choice. (6, 7, 9) It can be utilised to remove blood and thrombus, to localize and identify the source of the active bleeding, and to treat the bleeding through a variety of bronchoscopic techniques. (6) In addition to flexible bronchoscopy, a CT of the chest (with and without contrast) is performed to help localize the bleed and identify the etiology. (6, 8)

4.4 | Management of LTH

1. **Bronchoscopic Interventions** Multiple bronchoscopic techniques can be used to control the pulmonary hemorrhage such as iced saline lavage or tranexamic acid, topical medications (vasoconstrictive agents), balloon tamponade or bronchial blockade, and local thermal ablative therapies. (6, 8)
2. **Bronchial Artery Embolization (BAE)** In up to 90% of hemoptysis cases, the bronchial arteries are the source of the bleed. First, arteriography is performed in order to search for abnormal vascular structure or a hypervascularized site with tortuous vessels. Embolization is achieved by inserting occlusive material into the pathological vessel or the one supplying it, in order to stop the bleeding. (6, 8)
3. **Surgical Treatment** Surgery is required for patients whose origin of bleeding is identified and can only be treated with surgical intervention. (3)
4. **Other treatment methods** Extracorporeal membrane oxygenation can be a lifesaving strategy in pa-

tients with severe lung injury and profound hypoxemia. (10)

5 | APPROACH TO NON-LIFE-THREATENING HEMOPTYSIS

5.1 | History & Physical Examination

The patient's history must include an assessment of the frequency, severity, and the quantity of the hemoptysis. Associated symptoms, comorbidities, and risk factors for lung cancer including smoking and exposure to asbestos should be explored. (2) Certain historical findings can help narrow down the differential diagnosis. (3, 4)

A review of medications with a focus on anticoagulants and family history of bleeding disorders can assess the possibility of coagulopathy. Cough can be associated with bronchiectasis, chronic obstructive pulmonary disease (COPD), foreign body aspiration, pneumonia, and tuberculosis (TB). (4) The presence of fever can suggest bronchitis, pneumonia, lung abscess, neoplasm, pulmonary embolism (PE), and TB. (4) Sputum production is found in patients presenting with bronchiectasis, COPD, pneumonia, and TB. (4) History of smoking can be suggestive of bronchitis, COPD, and neoplasm. (4)

Immunosuppressed patients are at increased risk of lung abscess, pneumonia, and TB. (4) Recent diagnostic manipulation in the airways or foreign body aspiration could be a source of injury and subsequent infection (1). If the patient has been recently immobilised, PE should be considered. (3, 4)

The physical examination consists of evaluating the degree of respiratory distress (presence of tachypnea, cyanosis, use of accessory muscles of respiration) and the hemodynamic stability of the patient. We can also look for cues of pulmonary disease, cardiac disease, and other systemic diseases. (2) Clubbing of the digits is found in patients with lung cancer. Asymmetric peripheral edema can indicate the presence of deep vein thrombosis.

5.2 | Imaging

5.2.1 CXR is suggested as a first-line investigation for all patients with hemoptysis. (5) It is quick, readily available, and cheap. It determines the site of bleeding in 45-65% of the cases and is the cause in 25-35% of the cases. (1)

For patients with normal CXR presenting with minimal hemoptysis, a likely infectious or a benign cause, and no risk factors for lung malignancy, further evaluation can be deferred. (2) Patients with a suspected viral infection are observed and patients with a suspected bacterial infection are treated with antibiotics. (2) In case of recurrence or persistence of the hemoptysis, further investigation with CT or bronchoscopy is needed.

For patients with normal CXR presenting with active hemoptysis, without a clear or benign cause, a CT scan with contrast is warranted. If a clear diagnosis is not established, flexible bronchoscopy can be considered. (2)

For patients with normal CXR presenting with recurrent hemoptysis, a CT scan is recommended. (2) The most common causes for recurrent hemoptysis in patients with a normal CXR are bronchiectasis, carcinoid tumors, catamenial hemoptysis, and pulmonary arteriovenous malformation. (2) Pulmonary malignancies can be found in 10% of patients with risk factors for lung cancer who present with a normal CXR. (1)

5.2.2 CT scan with contrast is recommended for investigation of the origin and the etiology of hemoptysis. (10) Analysis of thin sections is necessary to adequately evaluate for bronchiectasis. (1) CT can help guide an embolization procedure to treat the hemoptysis. (1) PE is a rare cause of hemoptysis and when suspected should be evaluated with CT pulmonary angiography. (2)

5.2.3 Flexible bronchoscopy can be performed at the bedside and can be useful in securing the patient's airway if necessary. (1, 10) It also allows for endobronchial treatment procedures and obtaining pathologic or cytologic specimens. (2)

5.3 | Laboratory Studies

5.3.1 Hemoglobin and hematocrit can assist in assessing the chronicity and/or severity of the blood loss. Again, note that the main danger of acute hemoptysis is asphyxiation rather than blood loss. (2)

5.3.2 White blood cell count and differential can indicate the presence of an infection. (2)

5.3.3 Urinalysis and renal function tests are useful in screening for pulmonary renal syndromes including anti-glomerular basement membrane disease and granulomatosis with polyangiitis. (2)

5.3.4 Liver function tests and a coagulation profile are helpful in evaluating thrombocytopenia and other bleeding disorders. (2)

5.3.5 Sputum culture including mycobacterial culture can be ordered, when infectious etiology is suspected. (2) If TB is suspected, acid-fast bacillus smear should be done 3 times, as well as PCR test when available.

5.3.6 Serologic testing such as antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM) antibodies, and antiphospholipid (APS) antibodies can be useful when autoimmune diseases are suspected, including systemic lupus erythematosus, granulomatosis with polyangiitis, anti-glomerular basement membrane disease and antiphospholipid antibody syndrome. (2)

5.4 | Management of Non-Life-Threatening Hemoptysis

The management of non-LTH consists of treating the underlying etiology. For instance, patients with infiltrate seen on CXR and signs and symptoms suggestive of pneumonia should be treated with antibiotics. (4) If viral etiology is suspected, the patient's condition should be observed. In the case of PE, the patient should be treated with anticoagulation. (12) Patients with COPD or bronchiectasis can be referred to respiratory medicine where they can be further assessed and treated. Importantly, non-LTH does not equate to non-life-threatening pathology. While certain pathologies may not present as imminent hemorrhage or asphyxiation, they may evolve into life-threatening pathologies (i.e. tracheoinnominate fistula).

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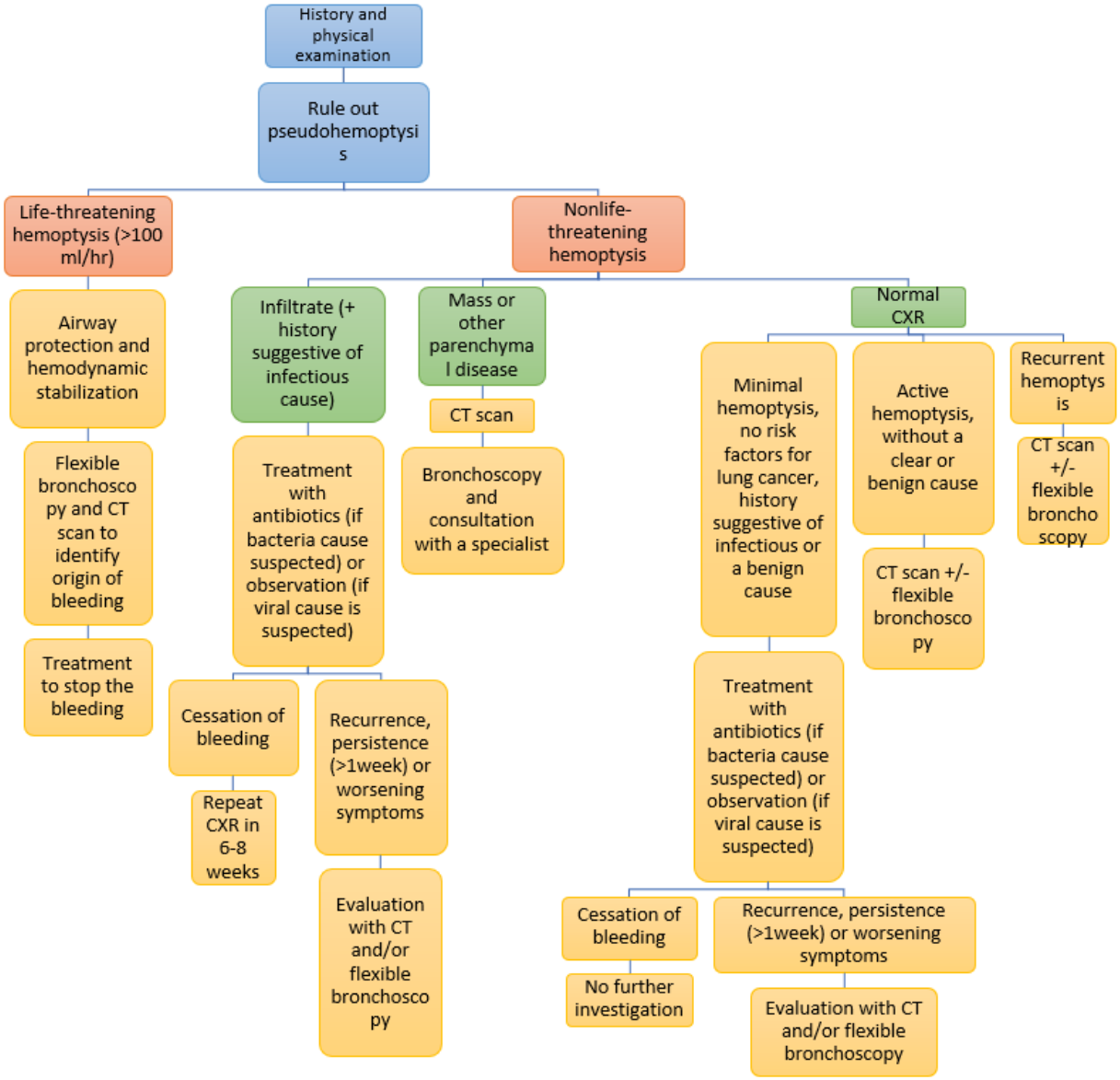

FLOWCHART 1 Approach to hemoptysis

APPROACH TO
McGill Journal of Medicine

Hyperkalemia

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ABSTRACT

Hyperkalemia is one of the most common electrolytic disorders encountered in clinical practice. Serum potassium concentration is tightly regulated by cellular transfer via insulin, catecholamines, and acid-base equilibrium and secondarily by the kidney via aldosterone and renal flow. Severe hyperkalemia can result in dangerous and potentially life-threatening manifestations, mainly cardiac in nature. It is therefore crucial for physicians to be able to identify the causes of hyperkalemia and provide appropriate treatment. This approach article provides an overview of potassium homeostasis, diagnostic strategies, and treatment guidelines for patients with mild, moderate, and severe hyperkalemia.

KEYWORDS
Hyperkalemia, ECG, chronic kidney disease, insulin, muscle paralysis

1 | QUESTION

A 72-year-old male presents to the emergency department with a three-hour history of nausea and generalized weakness. He is having difficulty walking and feels light-headed. The patient is known for congestive heart failure, hypertension, and type 2 diabetes mellitus for which he takes spironolactone, metoprolol, lisinopril, and metformin.

Vitals are as follows: Blood pressure 110/74, heart rate 118 beats per minute, respiratory rate 14 breaths per minute, oxygen (O2) saturation 98

Labs are as follows: CBC = hemoglobin 127g/L, platelets 260 x 109/L, white blood cells 7 x 109/L. Basic metabolic panel = Na 136 mmol/L, K 6.9 mmol/L, Cl 103 mmol/L, HCO3- 21 mmol/L, BUN 10 mmol/L, Cr 206 umol/L, glucose 5.8 mmol/L.

An electrocardiogram (ECG) was performed which showed ventricular tachycardia at a rate of 132 with diffuse tall, peaked T waves with a shortened QT interval.

What is the best next step in management of this patient?

(A) Chest x-ray
(B) Cation exchange resin
(C) Calcium therapy
(D) Furosemide
(E) IV bolus NS

2 | ANSWER

C. The patient has severe hyperkalemia (K = 6.9mmol/L) and requires urgent treatment. The patient has characteristic ECG changes (tall, peaked T waves with shortened QT), clinical manifestations (weakness, nausea), and a critical potassium serum level (>6.5mmol/L) which are each indications for urgent treatment. The patient should therefore be given calcium therapy, most commonly IV calcium gluconate, to antagonize membrane actions of hyperkalemia. A cation exchanger may also be given to help the body get rid of potassium. However, it is not the first step in management given its long onset of action and lack of direct cardiac protective effects (choice B). Though the patient is volume depleted and intravenous fluids may be indicated, the patient's hyperkalemia is of more urgent importance and should be treated first (choice E). Furosemide may help the body excrete potassium but is not indicated as it would exacerbate the patient's hypovolemia (choice D). Chest x-ray would not help in management of this patient's hyperkalemia (choice A).

3 | MAIN TEXT

3.1 | Definition and K Homeostasis

Potassium (K) is the body's main intracellular ion. (1) 98% of potassium is found in the intracellular space and the remaining 2% is in the extracellular space. (2) The normal range of serum K is 3.5-5.0 mmol/L. Hyperkalemia is defined as a serum potassium concentration of >5-5.5 mmol/L. (3) The large potassium gradient is maintained by Na-K ATPase pumps that drive sodium out of cells and potassium into cells. (4) This electrochemical gradient sets the resting membrane potential (RMP) at -90mV, which determines the threshold for muscle contraction. In hyperkalemia, there is a greater concentration of potassium, a cation, outside the cell, resulting in a more positive RMP and a lower threshold for depolarization. This leads to difficulty in cell repolarization, which results in manifestations in excitable tissues such as the heart, skeletal muscle, and nervous system. (3, 5)

3.2 | Etiology and Pathophysiology

There are many potential causes of hyperkalemia which may be divided into three main categories.

1) Increased K intake

Increased potassium intake may be due to overconsumption of potassium-rich foods, including potatoes, bananas, and avocados, or excessive amounts of potassium supplements or salt substitutes. (6) In healthy individuals, this is rarely the sole cause of hyperkalemia as the body is able to handle the potassium load by increasing potassium excretion. However, if there is underlying renal impairment such as in chronic kidney disease (CKD), the body may not be able to maintain potassium homeostasis and it may accumulate in the body. (7)

2) K shift into the extracellular space

Acute hyperkalemia may be due to redistribution of cellular potassium. (7) Shifting only 2% of the body's potassium can result in the doubling of serum potassium concentration. (2) Insulin and catecholamines are major regulators in potassium shifting. Small rises in extracellular fluid potassium concentration triggers insulin release which stimulates Na-K ATPases to uptake potassium into cells. (7) Consequently, insulin deficiency as in type 1 diabetes mellitus is a common cause of hyperkalemia. (8) Similarly, epinephrine binding to beta-adrenergic receptors causes ATP conversion to cAMP, which acts on Na-K ATPases to uptake potassium. Beta-blockers prevent beta-adrenergic stimulation, leading to less potassium uptake, which may cause hyperkalemia in patients with comorbidities such as renal insufficiency. (2) In some types of acidosis, such as hyperchloremic normal anion gap metabolic acidosis, the high serum hydrogen concentration is compensated for by exchange of hydrogen for potassium via cell membrane transport, leading to potassium secretion into the extracellular space. (2) In addition to cellular shifts in potassium, cell breakdown, such as in rhabdomyolysis, results in release of potassium into the extracellular fluid and may cause hyperkalemia. (1)

3) Impaired renal potassium excretion

While cellular shifts often cause transient hyperkalemia, impaired renal potassium excretion is the main cause of chronic elevations in potassium. (2) Potassium is freely filtered in the glomerulus and 70-80% is reabsorbed in the proximal tubule. Potassium excretion occurs at the level of the distal convoluted tubule and cortical collecting duct and is regulated by aldosterone. In hypoaldosteronism, such as in primary adrenal insufficiency, low aldosterone levels lead to low sodium absorption and low potassium excretion. Also, decreased distal urinary flow and reduced filtration, as in renal failure, leads to low levels of sodium reaching the collecting ducts and in turn low potassium excretion. (6) Drugs such as ACE-inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and non-steroidal anti-inflammatory drug (NSAIDs) may also cause hyperkalemia through their effects on the kidneys. ACE-Is and ARBs prevent angiotensin II formation and binding, respectively, which prevents angiotensin II's stimulatory effect on aldosterone secretion, decreasing potassium excretion. (9) NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), which convert arachidonic acid to prostacyclins, prostaglandins, and thromboxanes. (10) Prostacyclins, which are mediated by COX-2, increase potassium secretion at the distal convoluted tubule. Therefore, selective COX-2 inhibitors predispose a greater risk for hyperkalemia. (11) Additionally, potassium-sparing diuretics by definition cause the excretion of sodium and water in the urine while limiting potassium excretion, which may lead to hyperkalemia if overused. (12) There are two kinds of potassium-sparing diuretics that have distinct mechanisms of action. Aldosterone inhibitors, such as spironolactone and eplerenone, competitively bind to aldosterone receptors on the collecting duct and decrease the reabsorption of sodium and water, in turn decreasing potassium excretion. Sodium channel inhibitors, such as amiloride and triamterene, inhibit epithelial sodium channels (ENaC) in the distal tubule and collecting ducts, inhibiting sodium reabsorption and in turn potassium excretion. (12)

4 | INITIAL APPROACH

Evaluating a patient with hyperkalemia begins with ensuring a true increase in potassium. Pseudohyperkalemia is a term used to describe false elevations in potassium that do not reflect true serum potassium levels. (2) There are several mechanisms by which this can occur. The most common cause of pseudohyperkalemia is hemolysis from mechanical trauma, often secondary to difficult blood draws or the use of tourniquets. This causes rupture of erythrocytes and release of their contents, including potassium, in the serum. Potassium may also leak out of cells secondary to fist clenching, which is sometimes done during blood draws to make veins more prominent. In a minority of cases, pseudohyperkalemia may be due to platelet or white blood cell lysis which can occur in patients with thrombocytosis or leukocytosis as potassium leaks from platelet granules or leukocytes during coagulation. (4) Pseudohyperkalemia should be considered when there are no risk factors, manifestations, or apparent causes of hyperkalemia. Given that serum is the liquid part of blood obtained after coagulation, it may contain excess potassium secondary to lysis of damaged cells. Plasma, on the other hand, is the liquid part of blood after being treated with anticoagulants, which does not damage cells. Therefore, pseudohyperkalemia can be confirmed if the serum potassium concentration is at least 0.5mmol/L greater than the plasma potassium concentration. (2)

True hyperkalemia may require emergency treatment as it can be a life-threatening condition if not addressed promptly.(13) The urgency of treatment depends on clinical manifestations and degree of potassium elevation. The main clinical signs and symptoms include muscle weakness or paralysis and cardiac manifestations such as characteristic ECG changes, conduction abnormalities, and arrythmias. Other symptoms may include nausea, vomiting, diarrhea, dizziness, and palpitations. (7)

4.1 | History

It is crucial to obtain a focused history to determine the cause of hyperkalemia as it will affect patient manage-

ment. Important factors to address on history include potassium intake, exercise, crush injury, and medical history including renal disease, diabetes, and adrenal disease. (1, 14) In addition, obtaining a complete medication list can help identify medications that predispose to hyperkalemia such as beta-blockers, ACE-Is, ARBs, NSAIDs, potassium-sparing diuretics, digoxin, and recent intravenous potassium. (1, 2)

4.2 | ECG Changes

An electrocardiogram (ECG) should be performed in all patients with a serum K > 6 mmol/L and in all patients who are symptomatic, have rapid-onset hyperkalemia, or have underlying heart, liver, or kidney disease. (7) Hyperkalemia is associated with a variety of ECG changes in a dose-dependent manner. The first sign of hyperkalemia is tall, peaked T waves, usually seen when K levels are between 5.5-6.5 mmol/L. (15) Shortened QT and ST segment elevation may follow. As K rises to 7-8mmol/L or above, disappearance of P waves and QRS complex widening may develop. More severe changes can occur with levels > 8 mmol/L, including conduction blocks, ectopy, or sine wave pattern. (5) Hyperkalemia may also induce arrythmias, including sinus bradycardia, ventricular tachycardia, ventricular fibrillation, and asystole. (16) Treatment decisions should not solely be based on ECG changes as they are neither sensitive nor specific. (7) Though ECG changes may be variable, the rate of potassium rise is a greater predictor than the potassium serum level itself. For example, a patient with CKD who has chronically elevated potassium may not show the same ECG changes as a young type 1 diabetic patient who has an acute rise in serum potassium because of poor insulin compliance. (17)

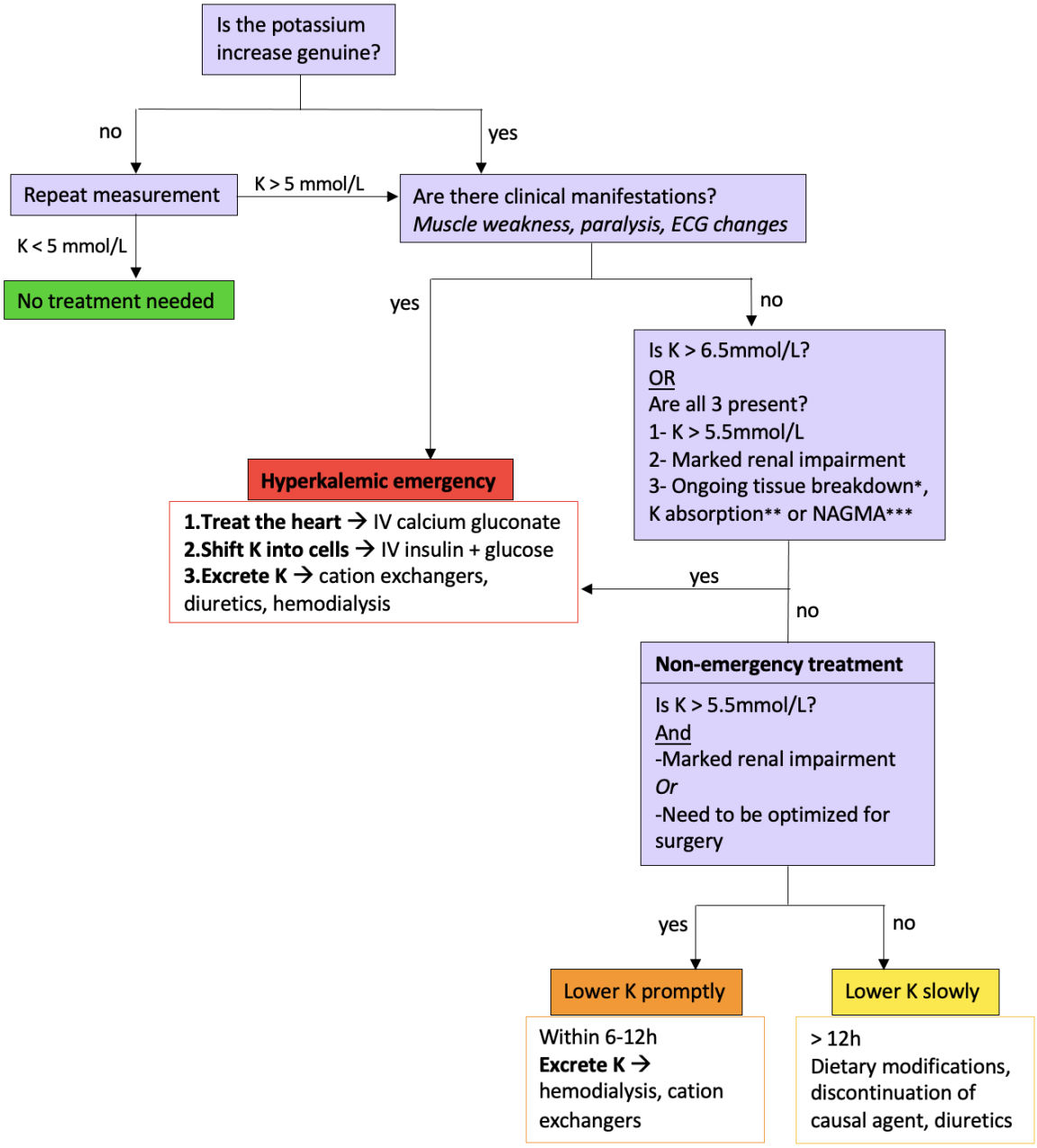
4.3 | Emergent Management of Hyperkalemia

Patients who have signs or symptoms of hyperkalemia (muscle weakness, paralysis, ECG changes) and/or serum potassium levels > 6.5 mmol/L require immediate management (Flow Chart 1). (13) Additionally, patients with serum potassium levels > 5.5 mmol/L with kidney function impairment and tissue breakdown (rhabdomyolysis, tumor lysis syndrome), significant non-anion gap metabolic acidosis, or ongoing potassium absorption (significant GI bleed) should also receive immediate treatment. The first step in treatment is administration of calcium therapy (most often IV calcium gluconate) as it raises the depolarization threshold of myocytes, stabilizing the cell membrane. (2) IV insulin should be given to shift potassium intracellularly. In order to avoid hypoglycemia, IV D50W infusion should be given in conjunction. (13) Other agents used to shift potassium intracellularly include beta-adrenergic agonists and sodium bicarbonate in patients with concurrent metabolic acidosis. (2, 7) Excess potassium can be removed from the body with a gastrointestinal potassium exchanger such as patiromer sorbitex calcium, sodium zirconium cyclosilicate (SZC), or sodium polystyrene sulfonate (SPS), or with thiazide diuretics if kidney function is intact. (18) Additional considerations include loop diuretics if volume-overloaded, dialysis if severe renal impairment is present, and discontinuing drugs that increase serum potassium (NSAIDs, beta-blockers, potassium-sparing diuretics). (13)

4.4 | Non-Emergent Management of Hyperkalemia

Some patients who do not fit the criteria for hyperkalemic emergency and therefore do not need calcium and insulin therapy still require prompt reduction of potassium within 6-12 hours. (19) These patients include those with K > 5.5 mmol/L who have significant renal impairment (ESRD or oliguria). The preferred treatment method is hemodialysis, which can normalize potassium within four hours and should be arranged as soon as possible. Another indication for prompt potassium reduction includes patients with a K > 5.5 mmol/L who are preparing for upcoming surgery. These patients can be managed with cation exchangers and reversal of the underlying cause of hyperkalemia. (19)

Patients with chronic, mild hyperkalemia (K<5.5mmol/L) or moderate (K = 5.5-6.5mmol/L)



FLOWCHART 1 *E.g., Crush injury, rhabdomyolysis, tumor lysis syndrome. **E.g., Significant gastrointestinal bleeding. ***Non-anion gap metabolic acidosis. Approach to Hyperkalemia Management. Adapted from: Treatment and prevention of hyperkalemia in adults. UpToDate ®.

hyperkalemia should have their potassium lowered slowly (over days to weeks). These patients often have CKD or use medications that inhibit the renin-angiotensin-aldosterone system (RAAS). (14) Treatment

includes dietary modification, loop or thiazide diuretics (as they cause potassium wasting), or discontinuation of the causal drug. (7)

5 | BEYOND THE INITIAL APPROACH

5.1 | Chronic Kidney Disease

Hyperkalemia is common in patients with CKD due to renal control of potassium. Potassium affects excitable tissues, leading to cardiac abnormalities. Recent evidence suggests that in CKD patients, hyperkalemia may affect neuromuscular tissues, which are also excitable, and result in peripheral neuropathy. (14) Peripheral neuropathy affects over half of CKD patients on dialysis. Therefore, optimizing potassium control may help improve neuromuscular outcomes in this population. CKD patients are usually treated with dietary modifications and cation exchange resins. Of note, sodium zirconium cyclosilicate (SZC) and patiromer sorbitex calcium are two treatments that have recently emerged as alternatives to sodium polystyrene sulfonate (SPS), which has been used for decades despite poor clinical evidence. (20) Sodium polystyrene sulfonate (SPS) has a gritty texture and an unpleasant taste, may cause diarrhea, and in rare cases, necrosis of the colon. The two newer agents have been shown to significantly reduce serum potassium levels and have a better taste than SPS, which may facilitate adherence and improve outcomes. (2)

6 | CONCLUSION

Hyperkalemia is one of the most common electrolyte abnormalities and is defined as a serum potassium concentration of > 5-5.5mmol/L. The main drivers of hyperkalemia are impaired intracellular potassium shifts and reduced renal potassium excretion. Hyperkalemia may be asymptomatic at lower levels but can cause potentially life-threatening cardiac arrythmias and paralysis at higher levels or when more acute. Patients with clinical manifestations, characteristic ECG changes, or serum K > 6.5 mmol/L should receive immediate treatment with IV calcium and IV insulin with glucose. Pseudohyperkalemia should always be excluded before treatment when there is no obvious cause or risk factors.

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APPROACH TO
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Acid Base Abnormalities

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ABSTRACT

This Approach To article provides an overview on acid-base imbalance, with a particular focus on metabolic acidosis. It provides a general step-wise approach on how to determine what acid-base imbalance is occurring and some of the potential underlying causes for each.

KEYWORDS
Acid-Base Disturbances, Acidemia, Alkalemia

1 | QUESTION

A 23-year-old male is brought to the Emergency Department by his mother. She reports that he has been acting strangely and is unable to answer her questions coherently. She adds that this all started after he was found sitting in the corner of the bathroom with his hands covering his ears, next to an empty bottle and blood-tinged vomit on the floor. On the way to the hospital, the patient reported nausea and severe abdominal pain. His mother notes that she has been feeling worried about her son given that he lost his job during the COVID-19 pandemic and has been severely depressed for several weeks.

You observe the following on examination:

General appearance: Diaphoretic

Neurologic: Not responding coherently to questions, complains of ringing in his ear

GI: Had another blood-tinged episode of vomiting, abdomen soft but has mild diffuse tenderness

Vital Signs: Temp: 37.7°C, HR: 122, BP: 144/96, RR: 28, Sat: 95% on RA

Labs: Na^+: 137 mEq/L *(N: 135-145)*, Cl^-: 90 mEq/L *(N: 98-107)*, K^+: 4.8 mEq/L *(N: 3.5-5.1)*, BUN: 5 *(N: 2.1-8.0)*, Glu: 7, Osmolality: 305 *(N: 275-295)*

Arterial Blood Gas: pH: 7.53 *(N: 7.38-7.46)*, $PaCO_2$: 18 mmHg *(N: 32-45)*, PO_2: 85 mm Hg *(N: 83- 116)*, HCO_3: 7 mEq *(N: 22-27)*

Normal Values as per the Medical Council of Canada indicated in brackets [1]

Which of the following is the most likely cause of the patient's condition and blood gas findings?

A. Salicylate intoxication
B. Opioid overdose
C. Diabetic ketoacidosis (DKA)
D. Alcohol overdose
E. Acetaminophen intoxication

2 | ANSWER

The patient in this case is mostly likely experiencing salicylate toxicity (A). Salicylate toxicity is characterized by a mixed acid-base disturbance presentation, in which the patient exhibits respiratory alkalosis *(salicylate directly stimulates the cerebral respiratory drive, leading to ↑ respiratory drive and consequent ↓ in CO_2)* and anion gap metabolic acidosis *(due to ↑ lactic acid, ketoacids and salicylic acid)*.[2,12] Respiratory alkalosis can be identified with ↑ pH > 7.45 and ↓ PaCO2 < 32-35. Metabolic acidosis can be identified by an anion gap of 40 *(Anion Gap = Na - [Cl + HCO_3]; N: 10-12)* indicating the presence of unbuffered acids. Early clinical features of salicylate toxicity include tinnitus (ringing of the ears) and irritation of the GI tract which can lead to nausea, vomiting and abdominal pain and tachypnea.[2] Later signs include agitation, delirium and seizures.[2,12]

3 | INITIAL APPROACH

Normal serum pH is tightly controlled within a range of 7.38-7.46[1] *(Note: These values can vary between institutions; many books will use 7.35 as the lower limit)*. Maintenance within this range is essential for normal protein and enzymatic activity. Alterations of the serum pH can lead to disruption of cellular functions required for survival. Metabolism in the body produces large amounts of volatile and non-volatile acids. Volatile acids include CO_2 derived from the breakdown of carbohydrates and fats, which can bind with water to form carbonic acid. CO_2 levels are controlled by alveolar ventilation. Non-volatile acids are derived from a few sources, including protein metabolism. These acids are eliminated in a 2-step process: 1) Acids combine with buffers such as extracellular bicarbonate (HCO_3^-), intracellular phosphate (HPO_4^{2-}) and carbonate in bones and 2) Kidneys excrete surplus of H^+ and reabsorbs HCO_3^{3-}.

Using these concepts, it is possible to approach acid-base disturbances using a step wise approach. This article will explore the approach that can be used to determine whether a patient is presenting with a simple or mixed acid-base disturbance.

Stepwise Approach to Acid-Base Disorders

Step 1: Establish the primary diagnosis[4,5]

- Look at the pH and determine whether there is an acidemia or alkalemia present:
  - Acidemia: pH < 7.35 (~7.38 per MCC)[1]
  - Alkalemia: pH > 7.45
- Look at the $PaCO_2$ and determine if the disturbance is respiratory or metabolic:
  - If $PaCO_2$ moves in the opposite direction of pH → Respiratory Process
  - If $PaCO_2$ moves in the saME direction as pH → MEtabolic Process

Step 2: Assess the degree of compensation[4,5]

Use the ratios listed in Table 1 to determine whether there is adequate compensation. If there is insufficient compensation, there is a greater chance that more than one acid-base disorder is present.

Step 3: Measure the following values *(especially important in metabolic acidosis)*[4,5]

The **Anion gap**. Normally, anions are present in our bodies and act as buffers for the cations that are present; mainly Na^+. These anions include proteins, circulating phosphates and sulphates, and albumin. It is important to note that some anions, such as pathological proteins, cannot be measured by routine labs.[6] When an excess of acids are present due to any pathologic condition, a gap forms between the number of acids present and the number of anions available to buffer them. In other words, an insufficient number of anions are present to act as buffers.

- The formula for the anion gap is **(AG= $[Na^+]$- ($[Cl^-]$ + $[HCO_3^-]$)**
- The normal value for the anion gap is 12 mEq/L [4,5,6]

If the anion gap is elevated, the **osmolal gap** must be calculated to determine if the underlying cause of elevated acid levels can be attributed to excess alcohol present in the body. The exact alcohols will be specified later in this article.

- The formula for the osmolal gap is **(Measured Osmolality on lab) – (Calculated Osmolality)**.
- The formula for the **calculated osmolality = 2$[Na^+]$ + [Glucose] + [Urea]**.
- The normal value for osmolal gap is <10.4

If the anion gap is elevated, the **Delta anion gap/delta HCO_3^- ratio** can be calculated to compare the change in anion gap to the change in $[HCO_3^-]$. An increase in acid content, reflected by a high anion gap, will cause the $[HCO_3^-]$ to decrease as it will act as a buffer for the excess acids. Therefore, the increase in acid levels is normally proportional to the decrease in $[HCO_3^-]$, rendering the delta anion gap/delta HCO_3^- ratio to be usually 1:1 or between 1 to 2.[4,7]

- The formula used to calculate delta anion gap/delta HCO_3^- is $$\frac{|(\textbf{NormalAGvalue}) - (\textbf{MeasuredAG})|}{|(\textbf{Normal}HCO_3^-\textbf{value}) - (\textbf{Measured}HCO_3^-\textbf{value})|}$$
- If the ratio <1, this implies that there is a greater loss in HCO_3^- than expected via compensation. Therefore, a concurrent non-anion gap metabolic acidosis process is present.[4] For instance, a patient presenting with DKA and profuse diarrhea will exhibit a ratio <1.
- If the ratio is >2, this implies that $[HCO_3^-]$ value has not decreased as expected, and there is a concurrent metabolic alkalosis or an elevated HCO_3^- at baseline as a result of chronic respiratory acidosis.[4, 7] For instance, this can be seen in a patient presenting with DKA and profuse vomiting of acidic gastric content.

Step 4: Establish the final diagnosis & determine underlying causes

While Table 2 is not an exhaustive list, it highlights some of the key causes for these disturbances.

4 | BEYOND THE INITIAL APPROACH

4.1 | Metabolic Acidosis

Metabolic acidosis is more complex than the other acid-base disturbances because it is further subdivided into two categories: 1) **High anion gap metabolic acidosis (AGMA)** and 2) **Non-anion gap metabolic acidosis (NAGMA)**. As explained earlier, the increase in the anion gap occurs due to the presence of excess acids. Many etiologies can account for this increase in acid content, and these etiologies can be remembered using the commonly used acronym "**MUDPILES**" (*see Table 2*). The following text expands on these etiologies.

Methanol, Propylene, Ethylene glycol intoxication

Ingested toxic alcohols such as methanol, propylene glycol and ethylene glycol are metabolized into organic acids that have significant side effects on the body, which can include causing metabolic acidosis.[9]

Uremia (reflecting renal failure)

In renal failure, a reduction in normal phosphate secretion increases hydrogen retention.[10] This process is further aggravated by impaired excretion of other substances such as organic anions and sulphates.[8]

Diabetic ketoacidosis

Ketoacidosis is a metabolic state in which there is a lack of glucose or an inability to use the glucose present, causing the body to break down fatty acids for fuel production.[11] This forms a high amount of ketone bodies, particularly acetone, acetoacetate, and beta-hydroxybutyric acid. This is commonly seen in: 1) diabetic ketoacidosis, 2) starvation and 3)excessive alcohol ingestion.[8,9,11]

Lactic acidosis

Lactic acidosis commonly occurs as a result of hypoperfusion to the tissues. This decrease in perfusion can be due to various causes, such as systemic hypotension secondary to shock.[9]

Salicylate overdose

Lastly, salicylate overdose is characterized by a mixed acid-base disturbance presentation. The patient will

have respiratory alkalosis because salicylates directly stimulate the cerebral respiratory drive, resulting in increased respiratory drive and consequent decrease in CO_2. There will also be an anion gap metabolic acidosis due to cumulative accumulation of lactic acid, ketoacids and salicylic acid.[12]

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5 | TABLES & FIGURES

Disorder	Primary Change	Compensatory Response
Respiratory Acidosis pH <7.35	↑ in CO2 due to ↓ in ventilation	Acute Response: • Rapid ↑ in [HCO_3^-] to buffer CO_2 • Compensation: ↑ 1 mEq/L HCO_3^- per 10 mmHg ↑ in $PaCO_2$ Chronic response *(requires 3-5 days to complete)*: • Kidney reabsorbs ↑ [HCO_3^-] in PCT and excretes more H^+ • Compensation: ↑ 3.5-4 mEq/L HCO_3^- per 10 mmHg ↑ in $PaCO_2$
Respiratory Alkalosis pH >7.35	↓ in CO2 due to ↑ ventilation	Acute Response: • Rapid ↓ in [HCO_3^-] to decrease buffering • Compensation: ↓ 2 mEq/L HCO_3^- per every 10 mmHg-change in $PaCO_2$ baseline Chronic response *(requires 3-5 days to complete)*: • Kidney produces less and excretes more HCO_3^- in resp. disorder lasting > mins-hours • Compensation: ↓ 4-5 mEq/L HCO_3^- per every 10 mmHg-change in $PaCO_2$ baseline
Metabolic Acidosis pH <7.35	↑ in acid content or ↓ in [HCO_3^-]	Acute Response *(begins within 30 min & completed within 12-24 hrs)*: • Hyperventilate (increased tidal volume or resp. rate) to expel CO_2 and decrease $PaCO_2$ • Compensation: ↓ 1.2 mmHg $PaCO_2$ per every 1 mEq/L ↓ HCO_3^-
Metabolic Alkalosis pH >7.45	↓ in acid content or ↑ in [HCO_3^-]	Acute Response: • Hypoventilate to retain CO_2 and ↑ $PaCO_2$ • Compensation: ↑ 0.6-0.7 mmHg $PaCO_2$ per 1 mEq/L ↓ HCO_3^-

TABLE 1 Different types of acid-base disorders, the associated primary change involved and the expected normal compensatory mechanism

Adapted from Table 5.2 in (Rennke & Denker, 2014)[3] using information from (Emmett & Palmer, 2020)[5]

Common etiologies[8]	
Respiratory Acidosis	Respiratory Alkalosis
• Primary pulmonary disease (e.g., COPD) • Drug Induced Hypoventilation (e.g., narcotics, sedatives, etc.) • Neuromuscular disorders (e.g., Myasthenia Gravis) • Respiratory Muscle fatigue (prolonged hyperventilation)	• Anxiety • Pulmonary Embolism • Pneumonia • Sepsis • Hypoxia • Mechanical ventilation • Pregnancy • Medication (e.g., Salicylate Toxicity)
Metabolic Acidosis *See "Beyond the Initial Approach" section below*	**Metabolic Alkalosis**
High Anion Gap Metabolic Acidosis: *TRICK: MUDPILES* • Methanol intoxication • Uremia (reflecting renal failure) • Diabetic ketoacidosis • Propylene glycol Intoxication • Isoniazid & Iron • Lactic Acidosis • Ethylene glycol intoxication • Salicylate overdose **Non-Anion Gap Metabolic Acidosis** • GI loss of HCO_3^-* – Diarrhea (most common cause) – Pancreatic Fistula • Renal loss of HCO_3^-* – Proximal tubular acidosis *aka Type 2 RTA* (↓ reabsorption) – Distal tubular Acidosis *aka Type 1 RTA* (↓ production) – Carbonic anhydrase inhibitors **differentiated using Urine AG*	**Associated with volume loss*- Loss of HCO_3^- and/or RAAS activation** • Gastric drainage • Vomiting acidic gastric content • Diuretics **Associated with volume expansion*-** • Adrenal disorders (Primary hyperaldosteronism) **Others causes**: • Severe hypokalemia • Impaired renal function • Iatrogenic (administration of bicarbonate) **differentiated using urine chloride*

TABLE 2 List of etiologies causing various types of acid-base disturbances

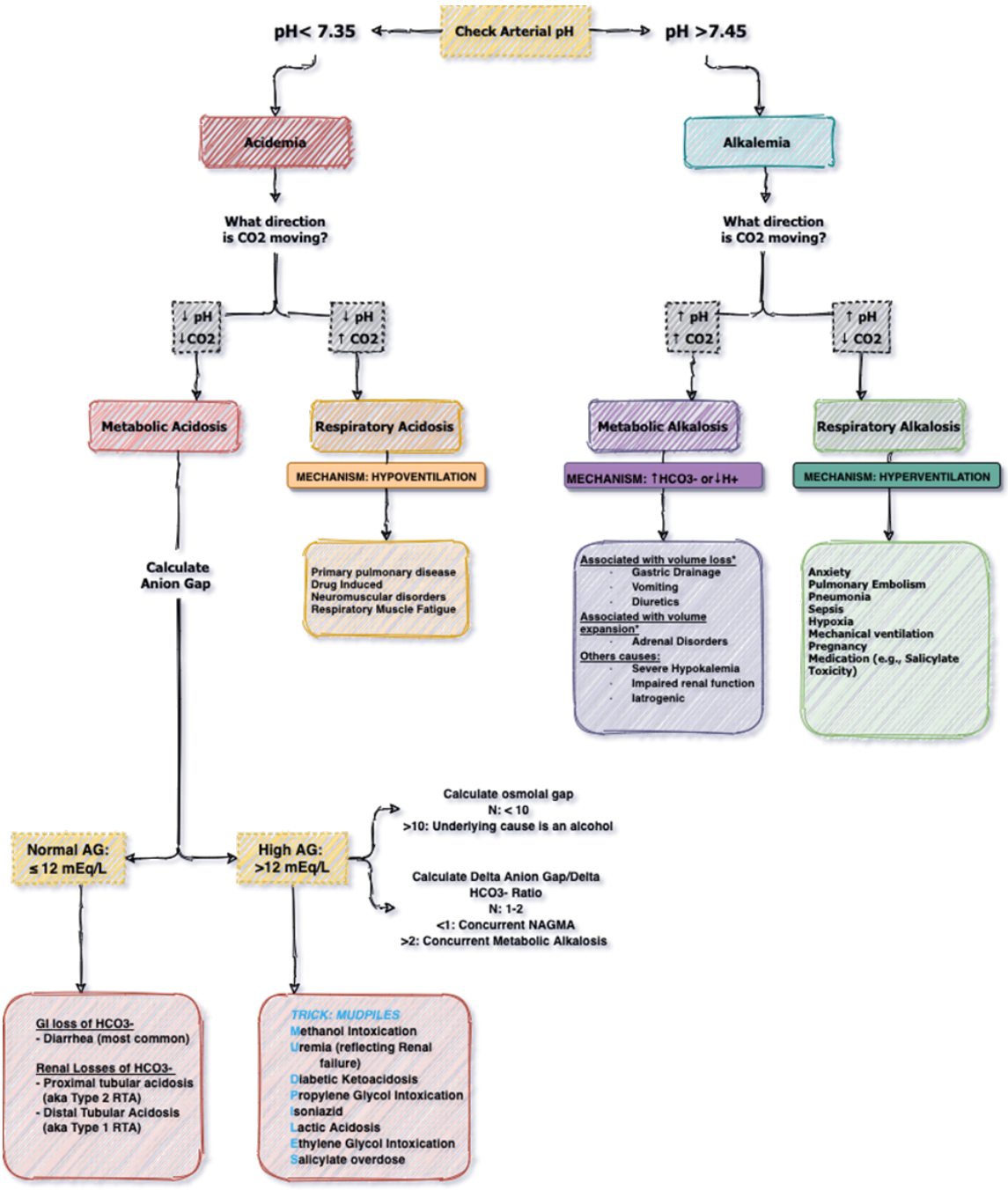

FIGURE 1 Summary of steps that can be used for acid-base disturbances. Inspired by Acidosis and Alkalosis Flowchart (Le et al., 2021)[13]

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