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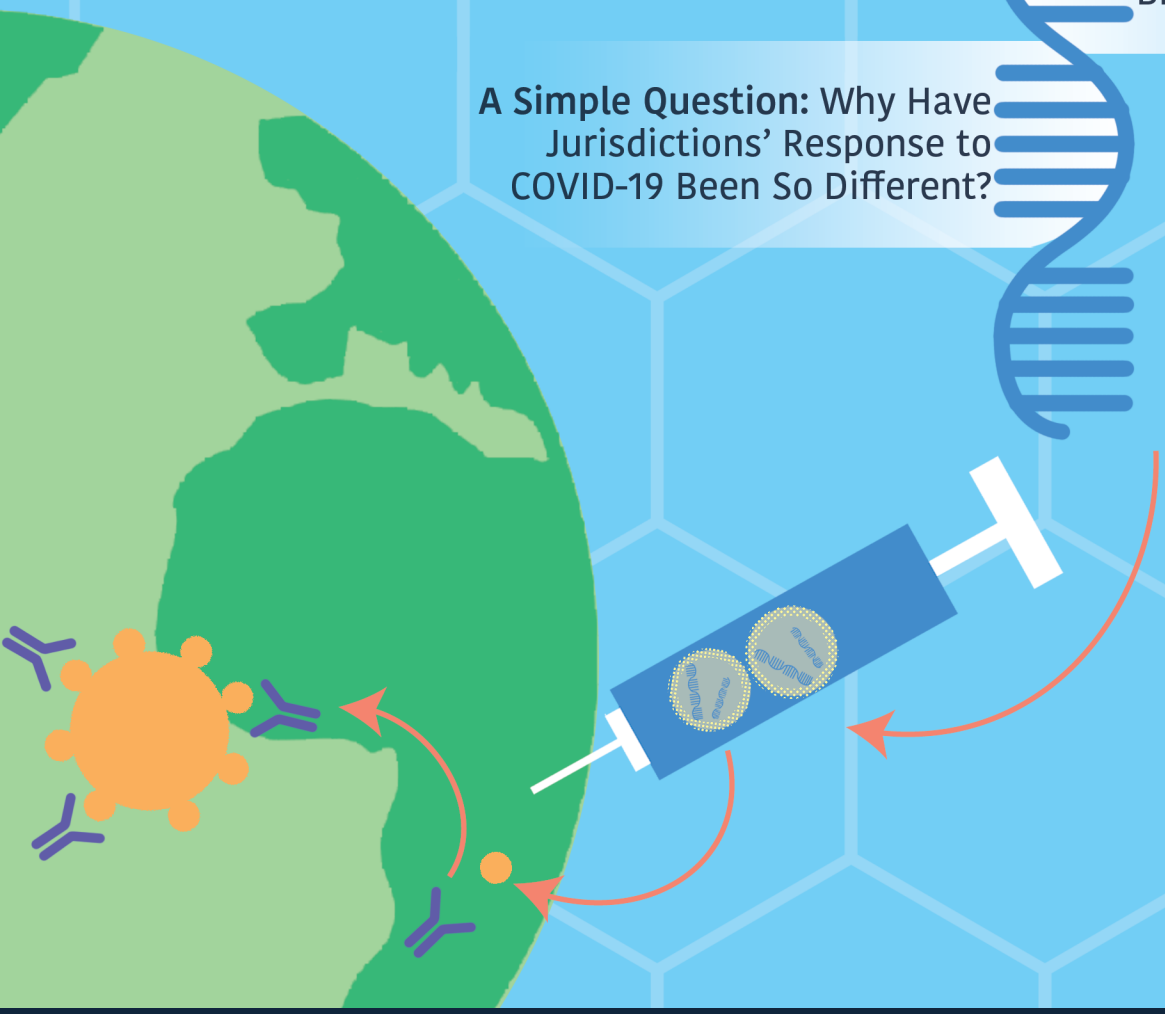

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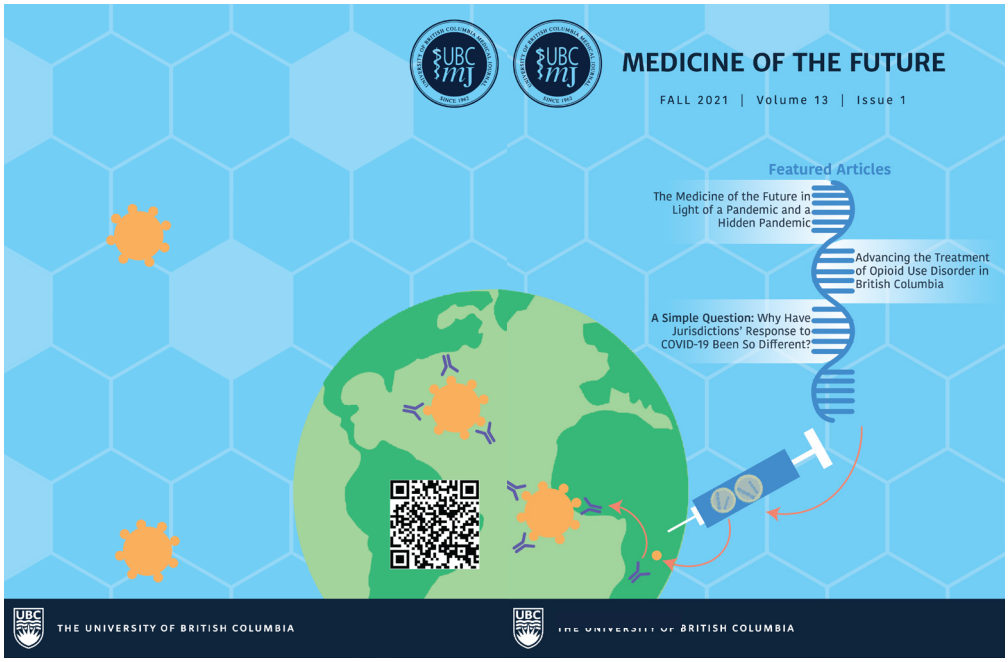
On the cover



In this issue, we explore the emerging advances in scientific research and technology that may revolutionize medicine in the future. These topics are the product of creativity, knowledge, and innovation used to improve the health of our population. For the cover art we chose to feature mRNA, the molecule used in the mRNA vaccines used to protect against the coronavirus 2019 disease (COVID-19). The mRNA vaccines are indisputably one of the most notable innovations recently that will continue to be used in other therapeutics, beyond COVID-19, to improve global health and the future well-being of the world's population.

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Medicine of the future

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The ongoing health crisis incited by the coronavirus disease 2019 (COVID-19) pandemic has led to significant consequences on global health and the future well-being of the world's population. Since 2019 when the first case of COVID-19 was diagnosed, the World Health Organization (WHO) has reported more than 212 million confirmed cases and has estimated that 4.4 million people have died from the disease.[1]

Despite its many challenges and tragedies, this pandemic has sparked numerous cutting-edge developments that may revolutionize the fields of science and medicine. Amidst the dark clouds of the pandemic, researchers around the world have discovered silver linings of innovation, collaboration, and discovery. Within months of the first reported COVID-19 case, researchers had already developed tools for diagnostic testing and began searching for ways to treat and prevent the disease.[2-4]

One of the most notable innovations during the past year was the COVID-19 messenger RNA (mRNA) vaccines. In December of 2020, Health Canada approved the use of the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines.[5-6] While this new technology might seem like a sudden breakthrough, the science behind these vaccines were built on decades of fundamental and applied scientific research. Since the 1990s, researchers have explored the possibility of unlocking the potential uses of synthetic mRNA in medicine.[7] During this time, other researchers studied the use of lipid nanoparticles for the safe and efficient delivery of medicine, including mRNA, into cells.[8] The remarkable convergence of these studies, in combination with the prompt genomic investigations of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein found on the surface of the virus that leads to COVID-19 disease[9-10], made the rapid development of these safe and effective mRNA-based vaccines possible. Within months of the first reported COVID-19 case, Pfizer-BioNTech and Moderna published studies of their mRNA vaccines that showed 94-95% efficacy in preventing symptomatic COVID-19 illness after two doses.[11-12]

At the time this editorial was written, more than 7.3 million COVID-19 vaccine doses have been administered in British Columbia (B.C.) and 84.4% of eligible British Columbians have received at least one dose of a COVID-19 vaccine.[13] Despite the constant evolution of the SARS-CoV-2 virus, both the mRNA and AstraZeneca vaccines remain highly effective against the Delta variant, the dominant variant of concern (VOC) that accounts for more than 95% of all positive COVID-19 tests in BC.[14] The simultaneous increase in vaccination rates and declines in COVID-19 case counts, hospitalizations, and mortality rates has allowed B.C. to gradually lift some of its province-wide restrictions.[15]

The COVID-19 vaccines may just be the beginning for mRNA-based therapeutics. Beyond COVID-19, mRNA vaccines could be deployed to protect against other deadly infectious diseases such as malaria, tuberculosis, and HIV.[16] In fact, researchers at the Yale School of Medicine have already published promising early results of their mRNA vaccine against malaria in mice.[17] Other than infectious diseases, there are also several clinical trials involving mRNA vaccines for cancer immunotherapy where the vaccines trigger the body's immune system to target specific cancer cells.[18]

Another major change in medicine during the pandemic was the drastic increase in the use of virtual health visits and telemedicine.[19] During the pandemic, telehealth was a safe alternative that allowed patients to seek medical care efficiently without the risk of acquiring or spreading COVID-19. In Ontario, office visits for primary care visits between March and July 2020 decreased by 79.1% while virtual care increased 56-fold compared with the same period in 2019.[20] According to surveys conducted by the Canadian Medical Association (CMA), 91% of patients were satisfied using virtual care[21] and 69% of Canadians would want to continue having access to telemedicine after the pandemic.[22] Furthermore, the 2021 National survey of Canadian Physicians reported that 7 out of 10 physicians are satisfied with telephone and video visits.[23] In the future, even in a post-pandemic state, telemedicine has the potential to allow patients to receive the supportive care they need at the comfort of their own homes while minimizing their exposure to other acutely ill patients. In addition, telemedicine could increase access to care in communities that are underserved by conventional medical practices. Although many businesses and services will slowly return to operate in offices and workplaces, it appears that telemedicine is poised to stay.

In the previous issue of the UBC Medical Journal, we invited authors to explore the theme of "Medicine in Times of Crises" and reflect on the wide-reaching consequences of the pandemic. This issue, however, will look ahead at solution-oriented strategies that will hopefully address existing gaps in medicine. Our first feature article by Dr. Michael Krausz, a Professor in Psychiatry whose research interests focus on comorbidity of severe mental illness and addiction, delves into the future of medicine in light of the COVID-19 pandemic as well as the overdose crisis, which is a prolonged public health emergency and the "hidden pandemic." Our second feature article by Dr. Paxton Bach, an addiction medicine physician and post-doctoral research fellow with the BC Centre on Substance Use, highlights advances in the treatment of opioid use disorder in British Columbia. Our final feature article by Dr. Peter Berman, a Professor in the UBC School of Population and Public Health, explores the varied outcomes in curbing COVID-19 around the world despite tackling the same disease and enforcing similar measures.

As many jurisdictions around the world, including British Columbia, begin to gradually return to a 'new normal' state, continued surveillance and constant modifications of health measures will inevitably be required to protect the health of our population. This pandemic has unraveled unprecedented acceleration of innovation and discovery. It has instigated an immense amount of international sharing and collaboration amongst clinicians and researchers globally. The rapid and exponential development of technology has proved that collaboratively, we can not only solve the challenges of this pandemic but also help address current disparities and sidestep future health crises.

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Conflict of interest

The authors have declared no conflict of interest.

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Advancing the treatment of opioid use disorder in British Columbia

Paxton Bach[1,2]

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Introduction

Drug poisonings have claimed the lives of over 90,000 North Americans in the past year alone, and the province of British Columbia (BC) is averaging more than 5 deaths per day due to an increasingly toxic unregulated drug supply.[1,2] These deaths represent only the tip of the iceberg when it comes to the morbidity and mortality attributable to untreated opioid use disorder (OUD), and should be an urgent call to action for health professionals across all disciplines.

Despite the magnitude of the problem, our current approach to the management of OUD in BC is fractured, leaving many patients struggling to find help when it is needed. In recent years harm reduction efforts have increased dramatically, but as a public health intervention it has still been embraced inconsistently, and it does not address many of the underlying fundamental issues.[3-5] Meanwhile, education around the treatment of substance use disorders is not prioritized, medications for the treatment of OUD are often inaccessible, and the treatment system as a whole lacks resources, consistency, and a willingness to adapt.[6-10] While many of these issues are structural and exist in a context of deep-seated and persistent stigma against people who use drugs, a number of BC initiatives and organizations are attempting to challenge this status quo and drive change through avenues such as education, research, and public health policy.

Education and Training

Exposure to the assessment and management of substance use and substance use disorders is lacking in medical school as well as in the majority of post-graduate education.[10] This has contributed to the fact that their treatment is often regarded as a niche area of practice, rather than a fundamental component of comprehensive medical care. There is evidence that this mentality is shifting, however, with growing interest the field being observed at multiple stages of medical training. The Addiction Medicine Consult Team at St. Paul's Hospital, for instance, has rapidly expanded its educational capacity and has seen exponential growth in the number of learners seeking out elective experiences in Addiction Medicine over the past decade. In the 2013-2014 academic year, only 4 trainees engaged in an elective with this specialty consult team, however by 2018-2019 this number had risen to over 200.[11] Ingraining these types of experiences into medical education is critical not only due to them providing a baseline level of knowledge, but because this type of exposure significantly increases a learners aspirations to incorporate the treatment of substance use disorders into their future clinical practice.[12]

In addition to expanded access to clinical rotations, the University of British Columbia has also participated in the recent nationwide Academic Medicine Responds to the Opioid Crisis project, helping to develop a national competency-based curriculum in the areas of pain management, substance use, and addictions. This training aims to bridge this knowledge gap for medical students across the country, and will soon be incorporated into the national licensing exam to ensure that a baseline level of knowledge becomes the standard for all Canadian medical graduates.

At a broader level, the British Columbia Centre on Substance Use (BCCSU) was established in 2017 with one of its core mandates being the provision of education and training in the treatment of substance use disorders at a provincial level. Since that time it has made a concerted effort to expand access to this type of education, with a number of initiatives specifically targeting an increase in the numbers of provincial prescribers of opioid agonist therapy (OAT) for the treatment of OUD. The progress has been dramatic, with a rise in the number of physicians prescribing OAT from 427 to 1682 since 2015, and the number of patients receiving a prescription for any form of OAT from 14,743 to 24,131 over that same span.[13] Though prescriptions for OAT are a crude measure of success in the treatment of OUD, the numbers are nonetheless encouraging, and a testament to the impact that can be made if/when we choose to make a dedicated effort. Enhanced physician specialty training has also been made available through the BCCSU Clinical Addiction Medicine Fellowship, a one-year training program in Addiction Medicine that is now entering its ninth year. The size of this fellowship has increased over this time from 4 to 11 fellows annually, making it the largest Addiction Medicine fellowship in North America by a wide margin, and once again demonstrating the rising level of interest in this important area of medicine.

Research and Innovation

While education remains a cornerstone for any significant and persistent change in the treatment of substance use disorders, there also is a desperate need for robust, empiric evidence to guide best practices. Current treatment options for those who are interested in accessing OAT are limited, and retention rates in treatment are often underwhelming.[7,9] Additional tools and techniques are required in order to offer patients a choice in when, where, and how they might access evidence-based treatment, and/or reduce their risk of overdose death and other harms.

Vancouver has a legacy of innovation in the world of substance use research, and has been home to numerous landmark North American trials studying paradigm-shifting interventions such as supervised injection facilities and injectable opioid agonist therapy.[14,15] More recently, a variety of ongoing clinical trials are destined to provide us with improved approaches for the treatment of OUD and reduction in risk of overdose death. Examples include the pRESTO trial, led by researchers from the BCCSU and representing the largest and most rigorous randomized control trial to ever evaluate the effectiveness of slow-release oral morphine in the treatment of OUD.[16] Critical areas of research that are actively being explored elsewhere include an examination of novel methods for initiating existing forms of OAT, an evaluation of how such methods can be implemented in non-traditional settings like the emergency department, and investigations into new alternative forms of OAT such as the transdermal fentanyl patch.[17-19]

On a more exploratory front, the provincial government of BC

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is increasingly endorsing the concept of "safe supply", or the provision of prescribed pharmaceutical alternatives to the toxic drug supply as a means of reducing overdose risk. In its current form this approach is embedded within a medical model, meaning that physicians are still the gatekeepers for these substances, but it remains a radical departure from traditional measures focused on supply-side interventions and the criminalization of drug use. While generally considered distinct from conventional treatment strategies for OUD, a harm reduction approach such as this has never before been attempted anywhere else in the world, and accordingly is currently subject to intense scrutiny and close scientific evaluation.[20]

These examples represent only a fraction of the local research focused on substance use and addictions, but clearly seat Vancouver as a progressive voice in this conversation and hold promise to revolutionize the approach to opioid use, overdoses, and the management of OUD around the world.

A Call for Systems Change

Taken together, the increased momentum around research and education in the treatment of substance use disorders is a promising step towards improving the management of OUD and reducing deaths, but in isolation it will continue to place the emphasis on ending the overdose crisis on prescribers alone. Unfortunately, such a physician-centric approach will inevitably be insufficient, and any approaches that exclusively target the proximal causes of the overdose crisis are doomed to fail. Within our healthcare system, more emphasis must be placed on the development of a patient-centred addictions treatment system that is accessible, flexible, coordinated, and responds to the individual needs of patients. More importantly, however, is an acknowledgement that we as a society must begin to recognise and address the fundamental driving forces in the current crisis including items such as stigma, racism, poverty, housing instability, trauma, mental illness, and the consequences of prohibition. Recent movement towards the decriminalization of illegal substances in the city of Vancouver is a noteworthy start, but will still fall short of its goals without a critical and uncomfortable evaluation of our societal approaches to these ultimate causes.

Conclusion

By lives lost alone, the overdose crisis is the most significant public health disaster to affect BC in our generation. While there have been notable advances in terms of education and research, the crisis is continuing to worsen while entering its sixth year, and it is clear that our response thus far has been inadequate. There remains a profound need to attack the stigma that pervades our system, to implement and refine evidence-based treatment and harm reduction approaches, and to demonstrate an interest in developing coordinated solutions informed by the medical community, people with lived experience, and society as a whole. There is an overwhelming amount of work to be done. It is of the utmost importance that we address the situation with the gravity, volume of resources, and effort that it deserves if we ever hope to slow the ongoing catastrophe of overdose deaths.

Disclosures

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Conflict of interest

The author has declared no conflict of interest.

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Same disease, similar measures, varied outcomes: Research to improve understanding of why results in curbing COVID-19 has been so different across jurisdictions around the world?

Peter Berman[1], Shelly Keidar[1], Mahrukh Zahid[1], Md Zabir Hasan[1], David M. Patrick[1,2], and the UBC Working Group on Health Systems Response to COVID-19[1]
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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has impacted millions of peoples and has shifted the landscape of global health policy. Countries and sub-national jurisdictions have responded to the global threat with well-established public health and social measures (PHSM) to reduce the spread of the infection and with supplemental clinical measures to mitigate adverse health outcomes of the disease.[1-2] Widespread knowledge about relatively similar measures resulted in very different levels of success in containing the infection and managing its consequences. The translation of scientific evidence into policy and practice in different jurisdictions varied in terms of timing, the choice of interventions, and the intensity of PHSM implementation.[3-4]

The emergence of an infectious disease such as COVID-19 was anticipated. There was prior attention to preparedness. However, a 2019 global ranking of almost all countries' preparedness to address a pandemic like COVID-19[5] had little predictive value in relation to outcomes in 2020 and 2021. Those considered well-prepared had very different levels of success in containing the infection and managing its consequences.

COVID-19 offers an opportunity to acquire new knowledge to improve health systems' responses to pandemics. Our research team was intrigued by the question of "what other factors can explain the observed differences in measures' implementation and their results?" this crisis exposed the need to expand the scope of inquiry to include contextual factors such as governance processes that influence public health policy, clinical practice, health, and other outcomes.

We focused our attention on specific contextual determinants of decision-making, specifically the institutional, political, organizational, and governance (IPOG) factors that drive jurisdictional responses to the current global health threat. We believe IPOG factors can help explain the variability in responses and their outcomes. A growing body of international evidence comparing different countries' experiences supports this view.[6,7] We are studying the IPOG factors by employing a learning systems approach focussing on key decisions made in pandemic response. We hope that new learnings in this area will support better laws, regulations, and organizational design to enable more effective health systems in future crises.

Our approach to examining IPOG factors' effects on governance and decision-making processes

Since April 2020, our interdisciplinary University of British Columbia (UBC) Working Group on Health Systems Response to COVID-19,[8] led by Prof. Peter Berman, has been developing research on IPOG factors affecting governmental responses to COVID-19. Our group consists of faculty, staff, students, and research trainees from UBC with interests and expertise in population and public health, political science, infectious diseases, global health, economics, and integrative thinking. We have honed our conceptual framework and data-collection tools by sharing them openly with a new and growing network of global health experts, senior policy officials at the WHO and World Bank, and an interdisciplinary group of scholars from political science, economics, medicine, and public administration from Canada and around the world. These activities included a series of virtual roundtables with support from UBC's Peter Wall Institute for Advanced Studies.[9] Involving stakeholders in the research from its inception and our group's links with the British Columbia (BC) Centre for Disease Control enhances the likelihood of our research outputs being effectively used by our intended knowledge users: the citizens and government of BC. Figure 1 presents our conceptual framework to examine the IPOG factors influencing the COVID-19 response.

In the framework, Institutions encompass the formal and informal rules and practices that shape human interactions in a society giving rise to meaning, norms, and appropriateness of behavior.[10-12] Politics is the arena in societies where power is assigned and distributed and where important influences on decision-making regarding health and other topics of public interest occur.[13] The Organization component focuses on governmental public bodies, especially the organizations charged with public-health functions, as well as others in the health system.[14] We define governance as the decision-making processes occurring at the interface between politics and organizations, conditioned by institutional norms. We focus specifically on understanding decision-making processes and implementation of policies, directives,[15-16] and, ultimately, laws.

We hypothesize that IPOG factors have influenced critical decisions on the strategies and interventions, thus shaping the response to COVID-19 within countries and sub-national jurisdictions. This influence is reflected in the type of interventions selected, the timing of their implementation, and how widely and well interventions are implemented (termed "stringency"[17]). The decisions are taken, and the implementation they engender can then be associated with the health and social outcomes that follow.

Our conceptual framework is the foundation for a mixed-methods case study approach,[18-19] currently applied in different countries and sub-national jurisdictions. Our first project, a CIHR-funded case study on the BC response to COVID-19, is still ongoing.[20] A team of UBC researchers and students have been collecting and analyzing qualitative and quantitative data to understand how IPOG factors influenced key decision points in BC's response at different stages in the pandemic's

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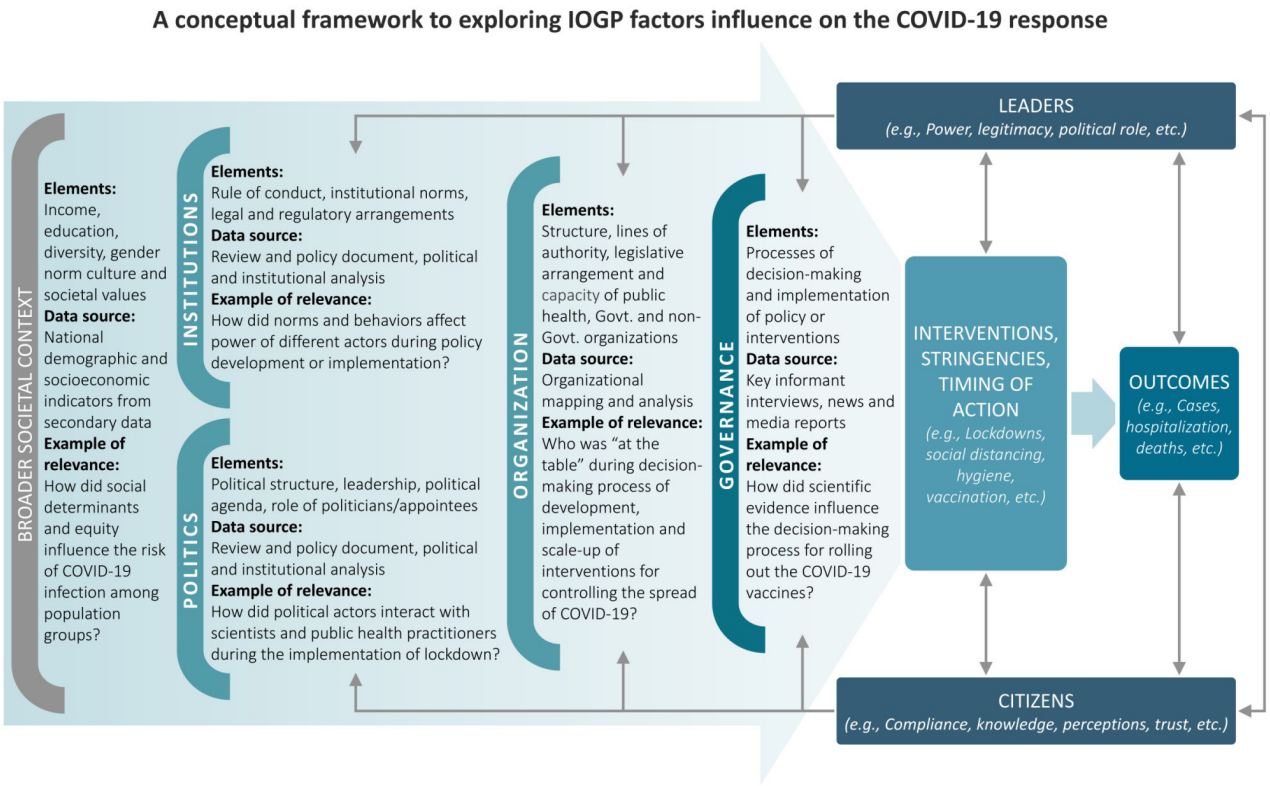

Figure 1 | A conceptual framework to examine the institutional, political, organizational, and governance (IPOG) factors influencing the COVID-19 response.

evolution. We have developed specific methods to identify key decision points in the pandemic's evolution, describe the organization of the public health system and its changes in response to the emergency. Confidential key informant interviews, using a structured interview guide, provide qualitative data and evidence on governance processes and associations with institutional and political factors.

While this work is underway, we have also initiated a research project with colleagues in several Canadian universities to compare and contrast provincial responses to COVID-19, applying the IPOG framework lens. Additionally, international partners in Peru, Brazil, Ethiopia, Bangladesh, India, and China have adapted our approach to conducting similar case studies in their context with potential comparisons.

We have also shared our efforts to strengthen the training of future public health leaders. Our team supported co-instructors Profs. Peter Berman and Milind Kandlikar in delivering a new masters-level course at UBC (SPPH 581Y, Term 2 in Academic Year 2020-2021).[21] This course resulted in five student-led case studies on jurisdictional responses, which provided some examples of IPOG influences on key decisions. One example described how Norway's relaxation of COVID-19 restrictions over the 2020-21 winter holidays - despite concerns about increased infections - was associated with political leaders' concerns about the adverse mental health effects of lockdowns and the importance of religious observance in majority communities.[22] Another example noted the weight South Africa gave to economic vulnerability in its majority population, due to the high prevalence of informal employment, in balancing equity relative to infection control.[23]

We are partnering with the UBC/BCCH Digital Lab[24] to develop an open-access platform to disseminate and support effective uptake of our research outputs by our BC knowledge users, as well as other national and international stakeholders. We hope that sharing our BC case study methodology, results, and other national and international research outputs on the platform will inspire Canadian and international teams to contribute to the growing body of knowledge on IPOG-related factors and improve the global response to COVID-19 and preparedness for future health crises.

We expect this type of in-depth analysis as part of different jurisdictional case studies, enhanced by comparative analysis, will strengthen understanding of how IPOG factors influence the effectiveness of responses. We think these will be among the questions leaders and the public will be seeking to answer once the acute crisis of COVID-19 has diminished. Ways in which laws, regulations, organizational structure can be improved and better education and training of public health professionals and political leaders are likely to get more attention as nations seek to prepare for the next pandemic. This work can help identify lessons learned and improve practices to strengthen preparedness for current and future health crises.

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Conflict of interest

The authors have declared no conflict of interest.

Ethics Approval

British Columbia, Peru, and Brazil Case Studies have recieved the approval of the UBC Behavioural Reserach Ethics Board as part of this work. Certificate # H20-02136.

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The medicine of the future in the light of a pandemic and a hidden pandemic

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Our greatest glory is not in never failing, but in rising every time we fall - Confucius

The SARS-CoV-2 has killed more than 4.2 million people worldwide, becoming one of the deadliest pandemics of the modern era along with the "Spanish Flu" and HIV/AIDS as of August 2021.[1] In the history of medicine, pandemics always challenged the healthcare system in a way that unveiled its weaknesses. As the virus spread, public health efforts, research, and frontline services had to move. However, as the number of cases has risen, the pandemic has exposed many vulnerabilities in the healthcare system, teaching us many lessons that will shape the future of medicine and our ability to face ongoing and future emergencies.

First, a global lens is essential for any proper understanding of medicine. The pandemic has spread rapidly through global travel without any regard for international borders, race, politics, and culture, forcing a global lockdown. Disparity in the impact of the pandemic on different nations and inconsistencies in the response of different healthcare systems to this pandemic offer critical lessons for the curious mind. Whether it is coordinating the supply chain of vaccines and personal protective equipment (PPE) or restricting human contact and travel, it is hard to imagine any sustainable success without international efforts, reminding the human race that "united we stand, divided we fall". Also, the comparison between countries and their health care systems is critical because it shows success and failure are manmade. As diseases do not discriminate and health is a universal right, medicine must be an international discipline in the frontline of humanitarian action.

Second, social determinants of health cannot be overemphasized. The unevenly distributed burden of coronavirus disease 2019 (COVID-19) across the globe besides other humanitarian crises such as Cholera epidemic in Yemen could be barely explained by biological differences, holding human race responsible for their mistakes in creating such disparities. While there is an emerging interest in social determinants of health in medical education, the burden of disease attributable to overcrowded living conditions, poor sanitation, poverty, homelessness, racism, and stigma overwhelmingly persists. This is visible from the disproportionate number of COVID cases in prisons and homeless population, or from the limited access to social services for those living in poverty due to lockdown.[2] Effective public health efforts and individual patient care must go beyond the biological model of medicine and integrate the housing, financial, racial, cultural, and political elements as part of patient advocacy.

Third, virtual care plays a major role in the future of healthcare. Although there was previously a significant resistance towards digital care, it has become incredibly popular globally.[3] Virtual care demonstrated improved the ease of access to care where patients can communicate with healthcare providers anywhere and anytime despite all the social distancing restrictions. However, we still have a long way to go – we must tailor our virtual platforms and electronic medical records (EMR) to various specialties and patients, solve the issue of incompatibility in the context of segmented provincial healthcare systems, and use the untapped potential of existing technology such as artificial intelligence.[4] As technology advances along with the ubiquity of smartphones and the Internet, there are plenty of opportunities to improve virtual care. We must take the lessons learned from the pandemic to continuously refine and improve virtual care for the betterment of healthcare.

Fourth, the pandemic has immensely affected our mental health, challenging our capacity to stay resilient to overcome this pandemic together. Immunocompromised individuals, such as the elderly, have faced constant fear of getting the virus. Healthcare providers have faced emotional distress from long hours, exposure to the virus, and shortages of PPE. The general population has faced social isolation and financial loss, commonly feeling anxiety, depression, boredom, and frustration.[5] In the US, during beginning of COVID-19 pandemic, prevalence of symptoms of anxiety disorder has risen three times the previous year, and four times for depressive symptoms, increasing the already high burden of mental illness.[6]

The pandemic has been a challenge for pre-existing mental health conditions. Finding a stable social network has become even more challenging given all the social distancing and limited opportunities to interact with others and maintain relationships. Outreach efforts were highly limited, leaving many patients with more severe forms of mental illness on their own as well. In addition, the heighted levels of distress due to fear of losing loved ones or self from COVID, and the constant fear of contracting the virus has severely challenged those with all sorts of mental illness ranging from mood disorders to schizophrenia.

Despite the growing burden of mental illnesses, some resources have been redirected away from psychiatric services to address the urgent needs for COVID-19 specific services in some jurisdictions. Although we have a global pandemic to manage, there is also an immediate need for improving the capacity of mental health resources by focussing on innovation (e.g. E-mental health), and including mental health as an agenda at the level of policies, education, and service provision. Mental health represents our capacity and resilience to collectively handle difficult situations, and by prioritizing it, will we have the strength to overcome future crises.

Finally, we must remember that we are also facing a far too prolonged public health emergency, the overdose crisis, "the hidden Pandemic". Our province has had a long painful journey related to poverty, homelessness, and substance use long before the overdose crisis, even before the HIV epidemic. There have been long struggles to advocate for harm reduction services such as needle exchange programs, safe injection facilities, and expansion of opioid agonist treatments, which would have been impossible without the relentless efforts of those with lived experiences. However, we still lack a proper mental health and addiction system to face these longstanding issues. Now, as we face dual public health emergencies, there have been significant concerns for the population severely affected by both crises as the

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number of deaths due to drugs reached the highest number this year in British Columbia (BC) past year.[7] Considering the comparable burdens of these two tragic crises, the much lower level of public attention and resources drawn to the overdose crisis is a sad reminder of profound stigma towards mental illness in particular substance use disorder in the society. The current system falls far short of the existing demands and there is an urgent need to ease access to care by expanding safe injection facilities, diacetylmorphine and hydromorphone assisted treatment sites like the Crosstown Clinic in Vancouver, mental health services, and decriminalization.[8] To achieve this, we have to overcome the stigma surrounding substance use and mobilize our resources that match the gravity of the situation.

In conclusion, the COVID-19 pandemic calls for a more dynamic and forward-thinking healthcare system as change will remain an integral part of the healthcare and similar challenges for the healthcare system will be inevitable in future. Although learning in class or in hospitals at a time of a global pandemic has been challenging for the medical students, it has also brought us unique opportunities to step back and figure out how we can do better. We have achieved historically the longest longevity and quality of life along with impressive victories against diseases like Polio, smallpox, and measles. Now, we face a high prevalence of chronic conditions such as mental illness, hypertension, obesity, and diabetes, which are intertwined with major social disparities across the globe, in the context of rapidly evolving technology and globalization. By applying the lessons we learn from this pandemic, we can overcome these issues and advance the field of medicine to the next stage.

Conflict of interest

The authors have declared no conflict of interest.

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Antihypertensive therapy in acute ischemic stroke

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Abstract

Ischemic stroke causes an acute hypertensive response in 60–80% of patients and is independently associated with poorer functional outcome. Despite the many advances in acute ischemic stroke (AIS) management, the use of antihypertensive therapy remains a controversial topic lacking consensus in several clinical settings. The use of antihypertensive agents and approach to blood pressure (BP) management will be discussed in the context of patients who are ineligible for acute reperfusion therapies and patients eligible for thrombolytic and endovascular reperfusion therapies. Consensus guidelines recommend active treatment for BP greater than 220 mmHg systolic, or 120 mmHg diastolic , unless the patient receives a thrombolytic in which case BP must be maintained below 185/110 mmHg. For endovascular therapy, it is recommended to reduce SBP to 140–180 mmHg. Intravenous labetalol and dihydropyridine calcium channel blockers (nicardipine and clevidipine) are good choices for therapy as they result in less BP variability, resulting in better outcomes.

Introduction

Stroke is the fourth-leading cause of death in Canada and is a major cause of disability, with over 400,000 people in Canada living with the long-term effects of stroke.[1,2] Approximately 62,000 people are treated for stroke or transient ischemic attack (TIA) in Canada annually.[3] Acute ischemic stroke (AIS) accounts for approximately 73–75% of all stroke cases in Canada.[4] Effective therapies currently include the use of tissue plasminogen activator (tPA) within 4.5 hours of ischemic stroke onset,[5] and endovascular therapy within six hours,[6] although specific functional imaging allows treatment up to 24 hours from stroke onset.[7]

There is a vast body of literature on the emergency department (ED) treatment of AIS, but clarity is still lacking regarding blood pressure (BP) targets and the choice of antihypertensive agent. AIS causes an acute hypertensive response in 60–80% of patients, and is independently associated with poorer functional outcome.[8] The International Society of Hypertension defines an acute hypertensive response as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg on two recordings, taken five minutes apart within 24 hours of symptom onset.[9] Avoiding excessively high BP and variability is important, but the threshold for initiation of antihypertensive agents remains less defined.

A major priority of AIS management is to salvage the ischemic penumbra by preserving collateral perfusion and using reperfusion strategies. Effective cerebral blood flow is dependent on the mean arterial pressure (MAP), and during AIS, effective cerebral adaptation to increased MAP is impaired.[10] High SBP is associated with intracranial hemorrhage and decreased functional ability after AIS. This is a challenging scenario for the physician as the specific BP needed to preserve the ischemic penumbra, while avoiding hemorrhagic transformation after reperfusion, is controversial. This article will review the literature surrounding the approach to hypertension in AIS.

Initial Management of Blood Pressure

The relationship between BP and outcome in AIS follows a U-shaped relationship where excessive elevation (SBP > 210–220 mmHg, MAP upper limit of approximately 140 mmHg) or depression (SBP < 130–155 mmHg, MAP < 90–100 mmHg) are associated with poorer outcomes.[11,12] Allowing elevated BP, or permissive hypertension, is commonly accepted in current practice to promote short-term improvement in collateral circulation to ischemic penumbra.[13]

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AIS guidelines only recommend treatment if SBP exceeds 220 mmHg, or if DBP exceeds 120 mmHg, with the exception of tPA thrombolysis, where BP should be < 185/110 mmHg.[14] A 2014 Cochrane review found no improvement in the outcomes of death, combined death or dependency, neurological deterioration, or quality of life with BP management beyond guideline recommendations during AIS regardless of class of medication used, dosage, intensity of lowering, or type of stroke.[3,15] In fact, some hazard was observed when using angiotensin-II receptor blocker (ARB) drugs in the SCAST trial,[15] involving 2029 patients, which found a slight increase in functional disability at six-month follow-up.[16] It also recommended that in patients already taking antihypertensive agents, it is reasonable to withhold them until the patient can tolerate oral agents without risk of aspiration, reinforcing the case for permissive hypertension.

Two trials demonstrated lower rates of death or dependency in patients who had their BP lowered within six hours of stroke onset, with greater benefit with earlier time to treatment. However, these findings cannot change current recommendations as the RIGHT trial only had 80 participants and included patients with hemorrhagic stroke,[17] while the INTERACT-2 trial studied hemorrhagic stroke.[18] However, these two studies have prompted further study into early initiation of BP-lowering treatment in AIS.

The subsequent RIGHT-2 trial studied the effect of lowering BP very early in management of AIS, TIA, and intracranial hemorrhage (ICH). Paramedics administered nitroglycerin in 1149 participants randomized within a median time of 73 minutes of stroke onset. No significant difference in 90-day functional outcome, death, or serious adverse events was found. In fact, there was a nonsignificant trend towards poorer outcomes in those with ICH, very early stroke (< 1 hour), or severe stroke (GCS < 12, NIHSS > 12) in the treatment group.[19]

The CATIS trial studied the reduction of BP by 10–25% in the first 24 hours and achievement of a BP <140/90 within 7 days.[20] 4071 participants with AIS with SBP between 140– 220 mmHg were randomized to antihypertensive therapy (including one of, or a combination of IV ACE inhibitors, calcium channel blockers, and/or diuretics), or no antihypertensive therapy (holding existing antihypertensives if necessary). They found no significant difference in death and major disability at the primary endpoint (14 days or hospital discharge), or secondary endpoint (three months).

The Canadian Stoke Best Practice Recommendations suggest to lower and sustain extreme BP elevations (e.g., SBP > 220 mmHg) by 15–25% over the first 24 hours, with gradual reduction to levels

Table 1 |Pharmacological options for management of BP in acute ischemic stroke.
Table adapted from 2019 update to 2018 AHA/ASA guidelines for management of patients with acute ischemic stroke.[14] Different treatment options may be appropriate for patients depending on individual comorbid conditions benefiting from rapid reductions in BP, e.g., acute coronary event, acute heart failure, aortic dissection or preeclampsia/eclampsia
*Note: In British Columbia only labetalol and hydralazine are available IV, and enalaprilat is only available orally as enalapril. Clevidipine is unavailable and nicardipine is only available by special access.

Patient otherwise eligible for emergency alteplase therapy except that BP is >185/110 mmHg
Labetalol 10-20 mg IV over 1-2 min. May repeat 1 time; or
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5-15 min, max 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
Clevidipine 1-2 mg/h IV, titrate by doubling dose every 2-5 min until desired BP reached; max 21 mg/h; or
Other agents (e.g., hydralazine, enalaprilat) may also be considered
If BP is not maintained ≤185/110 mmHg, do not administer alteplase
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP ≤180/105 mmHg
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6h, then every hour for 16h
If systolic BP >180-230 mmHg or diastolic BP >105-120 mmHg
Labetalol 10 mg IV followed by continuous IV infusion 2-8 mg/min; or
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5mg/h every 5-15 min, max 15 mg/h; or
Clevidipine 1-2 mg/h IV, titrate by doubling the dose every 2-5 min until desired BP reached; max 21 mg/h
If BP not controlled or diastolic BP >140 mmHg, consider IV sodium nitroprusside

consistent with long-term secondary stroke prevention.[3]

In terms of which antihypertensive agent to use, the American Heart Association/American Stroke Association guidelines recommend labetalol, nicardipine, or clevidipine. Hydralazine and enalaprilat may also be considered.[14] Agents should be chosen in a manner that avoids precipitous drops in blood pressure. Therefore, labetalol and the dihydropyridine calcium channel blockers (nicardipine and clevidipine) are preferred as they can be administered via continuous infusion, preventing the observed harmful effects of BP variability during AIS.[21] However, in British Columbia, only labetalol and hydralazine are available for parenteral use without special access (enalapril is only available orally). In British Columbia, clevidipine is unavailable and nicardipine requires special access. Dosing regimens detailed in Table 1 are based on general consensus as data do not show that one treatment strategy is superior.[14,22] Agents to avoid include propranolol and atenolol, which are associated with increased mortality, and nimodipine which is associated with worse neurological impairment and mortality in AIS.[23,24]

Of interest, magnesium sulfate has been studied for use in AIS for its neuroprotective potential. The FAST-MAG randomized control study looked at the pre-hospital administration of magnesium sulfate in suspected stroke: 73% of participants were ultimately diagnosed with ischemic stroke. The trial showed no significant difference between the magnesium sulfate and placebo groups in mortality or 90-day functional outcome.[25]

Blood Pressure Management with Intravenous Thrombolysis

When receiving thrombolytic therapy with tPA, SBP > 185 mmHg increases the risk of ICH. Symptomatic ICH is more common after thrombolytic therapy with higher SBP, and the odds ratio for ICH increases by 12–14% for every 10 mmHg increase in systolic BP post-thrombolysis.[26] The ideal blood pressure target for treatment with tPA is unknown although studies have attempted to address this.

A large 2019 systematic review and meta-analysis included 26 studies comprising 56,513 patients.[27] This study did not include trials that actively lowered BP, but studies that reported BP levels before and after thrombolytic therapy, and analyzed data retrospectively. This study demonstrated that higher pre- and post-thrombolysis SBP levels were independently associated with decreased likelihood of three month functional independence, and increased likelihood of symptomatic ICH. No association was found between pre- or post-treatment SBP and mortality, and lower pre-thrombolysis SBP did not increase successful arterial recanalization. Importantly, post-thrombolysis BP variability was related to higher likelihood of ICH, mortality and poor functional outcome. This is consistent with a NINDS trial post-hoc analysis which demonstrated that declines in SBP of > 50 mmHg or precipitous drops of > 30 mmHg were associated with poor outcomes, with acute drops of > 60 mmHg doubling the risk of death.[28]

The ENCHANTED trial randomized patients to intensive BP therapy (targeting SBP 130–140 mmHg) or to standard therapy (maintaining SBP < 180 mmHg) in early AIS management.[29] This trial studied 2196 tPA-eligible patients, who were randomized an average of 3.3 hours from stroke onset. There was no significant difference in functional status at 90 days, suggesting the safety of early intensive BP management. Although fewer patients in the intensive therapy group had ICH, the 90-day functional outcomes did not differ between the two groups. Importantly, there was only a difference of 6 mmHg between the groups, indicating that the trial may have been under-powered to assess a true difference.

The literature involving early BP management with thrombolytic therapy shows a decreased risk of ICH with BP control, but the evidence is inconsistent regarding improved functional outcome. Nevertheless, early BP management has been shown to be safe, and warrants further investigation. At this time the Canadian Stroke Best Practice Recommendations and American Heart Association/American Stroke Association guidelines both recommend treating BP > 185/110 mmHg before thrombolytic therapy and maintaining BP < 180/105 mmHg for 24 hours post-alteplase administration.[3,14]

Blood Pressure Management with Endovascular Therapy

Endovascular Therapy (EVT) is a valuable approach to improve outcomes in AIS. The 2018 Canadian stroke best practice guidelines recommend keeping SBP < 220 mmHg and DBP < 120 mmHg for EVT. A 2017 multicenter study demonstrated significantly higher mortality with SBP > 180 mmHg or < 110 mmHg in EVT.[30] The 2019 American Heart Association and American Stroke Association guidelines for the early management of AIS both advise maintaining BP ≤ 185/110 for patients awaiting thrombectomy who have not received IV fibrinolysis.[14]

A 2019 systematic review found that drops in MAP < 70-80 mmHg, or 10–40% from baseline led to poorer outcome with EVT.[31] A recent retrospective cohort study combining patient data from 3 randomized control trials found statistically worsened 90-day functional outcome associated with MAP < 70 mmHg for more than 10 minutes or < 90 mmHg for greater than 45 minutes.[32] Similar findings were observed in more recent clinical trials and retrospective studies.[33–37]

Higher SBP within 24 hours of EVT correlates with greater severity of hemorrhage within 48 hours, and worse 90-day functional outcome.[38] A 2017 single-center study demonstrated that reducing post-EVT BP below 160/90 mmHg significantly decreased 3-month mortality by 6.5% compared to the permissive hypertension group (<220/110 mmHg, or <180/110 mmHg for tPA-treated group).[39] BP variability is more common in patients with incomplete recanalization, and is associated with ICH and poorer outcome following EVT.[40]

Compared to thrombolytic therapy, less research has looked at BP in EVT; most studies are observational, and questions still remain regarding causal relationships, especially with the lack of randomized control trials in this area.[41] However, risks exist within the guideline recommendations for BP in EVT. The Society of Neuroscience in Anesthesiology and Critical Care recommends maintaining SBP between 140–180 mmHg during EVT, but highlights the importance of being highly vigilant of hypotension,[42] which not only leads to poorer outcomes, but also leads to vasopressor use which is a strong predictor of infarct growth.[37]

Another question that remains unanswered is in regard to the optimal BP after different levels of recanalization (measured using the thrombolysis in cerebral infarction (TICI) score).[43] A 2020 systematic review found that BP reduction post-EVT was inversely associated with worse outcomes in TICI 3 patients, but not in TICI 2B patients.[44]

Conclusions

No consensus in literature exists regarding when to initiate antihypertensive therapy in AIS. Guidelines derived from expert consensus recommend that BP should only be treated if SBP exceeds 220 mmHg, or if DBP exceeds 120 mmHg. In the context of thrombolytic therapy, BP must be kept below < 185/110 mmHg prior to administration of tPA.[3] Some evidence shows that early BP reduction beyond 185/110 may be safe, but further investigation is required. In the context of EVT, reducing SBP to 140–180 mmHg is suggested, but more randomized control trials studying antihypertensive use in EVT are needed. In all cases of AIS, the established association between BP variability and poor outcomes suggests that IV labetalol and the dihydropyridine calcium channel blockers (nicardipine and clevidipine) should be considered when treating BP, as these drugs have been found to cause lower BP variability than other agents.[21,27,28] Current evidence shows some support for early BP management beyond guideline recommendations. However, further study is required before clear thresholds for initiating antihypertensive therapy in AIS can be set.

Conflict of interest

The authors have declared no conflict of interest.

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Dyspepsia: a review of investigations and management for pre-clinical medical students

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Abstract

Dyspepsia is a common symptom encountered in the community setting with a large differential diagnosis and a heterogeneous pathophysiology. Due to its prevalence, dyspepsia is responsible for substantial health care costs in Canada and significantly affects quality of life. We present here a practical, evidence-based approach to dyspepsia with the goal of providing medical students with efficient guidelines to develop effective investigation and treatment plans in a clinical setting.

Dyspepsia

Patients with gastrointestinal disorders are seen at all levels of medical care including primary care, as hospital inpatients, and in long-term chronic care facilities. Each year, approximately 20 million people in Canada are affected by digestive disorders, which account for 10 percent of all hospitalizations.[1] It could be argued that the gastroenterology clinic curriculum could be augmented by specific teaching around dyspepsia. At the University of British Columbia for instance, the medical curriculum consists of 4.5 weeks of gastroenterology classroom teaching in the two years preceding clerkship. In Year 3 at the University of British Columbia's medical curriculum, only a single half-day is dedicated to outpatient gastroenterology. Year 3 rotations in CTU and family practice significantly vary in the quantity of gastroenterology exposure, with no guarantee that students will obtain equal and consistent teaching or training. The apparent deficiency in gastroenterology teaching in medical schools place newly transitioning junior residents at risk for potential knowledge gaps.[2]

One method to ensure medical undergraduates receive adequate gastroenterology education is to rectify insufficient teaching in the educational curriculum. We present here a practical approach to dyspepsia, with evidence-based guidelines. We hope that this approach will make it easier for pre-clinical medical students to evaluate the symptoms and signs of dyspepsia, while providing senior medical students with efficient guidelines to develop investigation and treatment plans in a clinical setting.

Dyspepsia refers to the constellation of symptoms of epigastric pain, heartburn, postprandial fullness (early satiety), nausea with or without vomiting, and belching lasting for at least one month or recurring frequently.[3] Many patients with dyspepsia also concomitantly complain of reflux symptoms (water brash, regurgitation). We have developed an easy-to-follow flowchart depicting the standard approach for medical students to dyspepsia (Figure 1). This diagram represents a US and Canadian secondary and tertiary care perspective on managing dyspepsia with pharmacological therapies and endoscopy.[3,4]

When a patient presents with symptoms of dyspepsia, obtaining a careful history is the most important first step. In acute presentations of dyspepsia with severe pain (such as in the Emergency Department), a prudent history is fundamental in distinguishing life-threatening mimics of dyspepsia. The three most common mimics of dyspepsia encountered in an emergency setting are myocardial infarction, cholecystitis, and pancreatitis. These ailments are often accompanied with other cardinal clinical features, as presented in Table 1.[5]

In the majority of dyspepsia cases, the symptoms are chronic and the patient presents in an outpatient setting. Taking a detailed history can reveal red flags such as vomiting, unintended weight loss of over 10% initial body weight, melena, or dysphagia. Depending on the patient's family history and other comorbidities, red flags may indicate underlying malignancy. The risk of malignancy is primarily associated with age, thus in light of the recommendations by Choosing Wisely Canada we set the age threshold for endoscopy to 60 years old even in the absence of red flags present.[4,7,8] This is a conditional recommendation set forth by the American Gastroenterology Association (AGA) and Canadian Association of Gastroenterology (CAG).[4] Ultimately, the decision to pursue endoscopy in earlier age groups should be determined by clinical judgment, by taking into account physical examination findings and laboratory studies. Findings that may provide clues to diagnose gastric cancer include the presence of anemia, occult blood in the stool, gastric

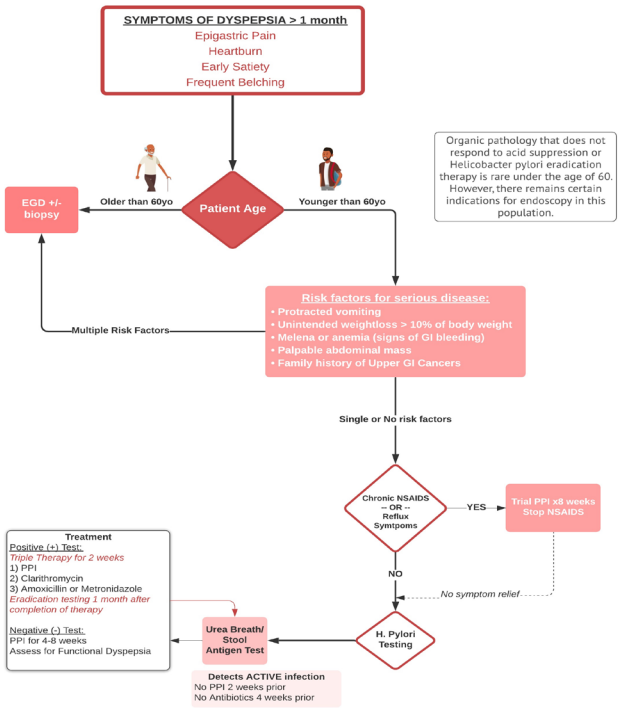

Figure 1 | A simplified approach to dyspepsia for pre-clinical medical students. The above diagram is a reference for pre-clinical students regarding the basic approach to dyspepsia in an outpatient setting. Abbreviations: EGD, esophagogastricduodenoscopy.

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Table 1 |Key clinical findings that distinguish dyspepsia of gastric origion from more sinister origins.

Myocardial Infarction	Cholecystitis	Pancreatitis
Exertional dyspnea,	**R**UQ* pain radiating to the epigastrium,	**E**pigastrium pain radiating to the back,
"**H**eavy" chest pain,	**M**urphy's sign,	**A**lleviated by sitting upright,
Abnormal ECG,	**P**rovoked by fatty foods,	**E**levated lipase blood levels,
Abnormal Troponins	**S**onographic evidence	**S**teatorrhea (fatty stools)

*RUQ = right upper quadrant

distension, or supraclavicular adenopathy. A mid-epigastric palpable mass or nodular liver may also be helpful in localizing pathology to the abdomen.[9] Unfortunately, the patient may also appear completely healthy on physical exam and bloodwork.

In younger patients, endoscopy is no longer recommended as a first-line investigation in the presence of a single red flag on history taking alone. A systematic review evaluating over 46,000 dyspepsia patients receiving upper GI endoscopy illustrated that red flags had limited value in detecting any organic pathology (malignancy, peptic ulcer disease, or esophagitis).[10,11] A single patient-reported red flag on thorough history taking also had a low sensitivity and specificity for malignancy, at approximately 66%.[12] Given the risk of underlying malignancy in younger cohorts is very low, <1% even with red flags, endoscopy is not a cost-effective investigation for dyspepsia in patients under 60 years old. However, it is imperative to obtain a complete history of the patient to understand the context of their ailment and evaluate all potential aggravating factors prior to finalizing an investigative plan.

For instance, patients who have immigrated to Canada from parts of Asia such as Thailand, Indonesia and the Philippines have a higher probability of *H. pylori* infection and hence gastritis, gastric ulcers, and gastric cancer—all of which require endoscopic visualization or tissue sampling for diagnosis.[13] Gastric malignancy has also been associated in young adults with a high intake of nitrates and salted meat and fish in their diets.[14] Recent travellers may return with dyspeptic symptoms such as nausea from infectious gastroenteritis or acute hepatitis. Family history cannot be overstated, as a family history positive for GI cancers prompts early investigation of dyspepsia with endoscopy, even in younger populations.[7] Social history may reveal underlying causes of emotional stress predisposing the patient to dyspepsia.

Once a thorough history is collected and age is identified for management stratification, the next step would be differentiating the three most common but non-malignant pathologies of dyspepsia: reflux esophagitis, gastritis, and peptic ulcer disease (PUD). Gastritis and PUD are commonly confused and understanding the distinctions is important as management and prognosis can vary significantly. Gastritis is the inflammation of the mucosa; that is, only the lining of the stomach (i.e., epithelium and lamina propria) is inflamed.[5] Occasionally, shallow sores called "erosions", which extend into the lamina propria but not into the muscularis mucosa, may develop.[8] Gastritis can be classified as acute or chronic. Acute gastritis is often associated with NSAIDs, acute alcohol intake, spicy foods, and early H. pylori infections. Chronic gastritis is associated most commonly with chronic H. pylori infections or chronic NSAID use. Diagnosis requires histology sample and treatment usually involves a prescription for a PPI and correcting the patient's lifestyle or medications.[5]

PUD is focal inflammation of the stomach or duodenum lining with ulceration extending into the muscularis mucosa and often into the submucosa.[16] An intense, localized pain is common and an ulcer may be complicated by the risk of bleeding, causing anemia or rarely perforation. Sometimes gastritis can lead to an ulcer if the causative agent is not treated (H. pylori infections begin as gastritis but can progress to PUD). The majority of gastric ulcers are caused by chronic H. pylori or chronic NSAID use.[15] Stress, smoking, spicy foods, and steroids do not cause ulcers, but are aggravating factors.

These three aforementioned most common etiologies of dyspepsia are secondary to gastroesophageal reflux disease (GERD), chronic NSAID use (including aspirin), or H. pylori infection. Up to 30% of patients with dyspepsia in a Canadian population were found to be taking chronic NSAIDS.[15] Thus for patients taking chronic NSAIDS, dose reduction or substitution of NSAIDs is often effective in treating their dyspepsia.[8] Those with reflux symptoms in the absence of NSAIDS should be trialed on a proton-pump inhibitor (PPI) for 8 weeks as it is therapeutic for GERD, gastritis, and PUD, and can be clinically diagnostic of GERD. Lifestyle modifications should be made in conjunction with PPIs, including avoiding trigger foods, weight loss, and smoking cessation. If PPIs fail to alleviate symptoms, the next step would be to order non-invasive H. Pylori testing. If the test is positive, treatment should be initiated. We have listed the traditional 2-week Triple Therapy approach as it illustrates the principles of treatment: antibiotics and gastric acid reduction. The standard course of triple therapy consists of clarithromycin with either metronidazole or amoxicillin plus a proton pump inhibitor (PPI), and is one of the most commonly used treatments for H. pylori.[17] A repeat H. Pylori test should be done one month after completion of treatment to prove eradication of the pathogen.[18]

If the initial H. Pylori test is negative, the pathology is likely functional dyspepsia.[4] Functional dyspepsia refers to dyspepsia that has had all investigations return as negative for organic causes. A workup for depression and anxiety should be considered in these cases. Management of functional dyspepsia is similar to that for GERD, which utilizes proton-pump inhibitors and emphasizes lifestyle modifications.[8]

Dyspepsia is a common symptom with a large differential diagnosis and a heterogeneous pathophysiology. Dyspepsia is responsible for substantial health care costs and significantly affects quality of life. With our discussion we present a practical approach to dyspepsia, with evidence-based guidelines. We hope that this approach will make it easier for pre-clinical medical students to evaluate the symptoms and signs of dyspepsia, while providing senior medical students with efficient guidelines to develop investigation and treatment plans in a clinical setting. For medical students, education is an important component of healthcare, enabling active engagement in the responsible management of patient health.

Conflict of interest

The author has declared no conflict of interest.

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A literature review of impact of social determinants of health on preventative oral health program design in remote communities: A focus on Spiti Valley, India

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Abstract

Background and purpose: Dental caries is the most prevalent pediatric illness worldwide. It results from a complex interplay between biological and social determinants of health (SDH). The purpose of this review is 1) to understand the social determinants of health impacting dental caries burden in remote communities, using Spiti Valley, India as an example; 2) to understand the importance of using SDH to inform preventative oral health program (OHP) design, and lastly; 3) to provide best practice guidelines for implementing OHPs in remote communities worldwide.

Methods: MEDLINE and PubMed databases were searched for English-language articles describing oral health programs implemented in remote communities around the world. Articles pertaining to OHPs that used preventative interventions to address pediatric dental caries in remote communities were included. Articles were excluded if the study sample included special needs children, and if the program lacked preventative interventions.

Results: Remote communities around the world share many SDH factors, such as low income, limited education, limited availability and access to oral healthcare services, nutritious foods, clean water, and electricity. These factors are key to informing OHP design, and when addressed appropriately, can reduce a community's dental caries burden.

Conclusion: There is a continued need for preventative OHPs in remote communities worldwide. In communities such as Spiti Valley, India where the pediatric caries burden remains high despite caries prevention strategies, efforts are needed to identify and address SDH factors, like cariogenic diets, that continue to contribute towards dental caries formation.

Introduction

Dental caries is the most prevalent pediatric disease,[1] affecting 573 million children worldwide.[2] When left untreated it can lead to pain, infection, difficulty eating and sleeping, adverse growth patterns, behavioural problems, and absences from school.[1] In addition, caries in the primary dentition is a significant predictor of future caries in the permanent dentition.[3] Most of the affected children reside in remote and rural communities, where oral healthcare resources are extremely limited.[1] An example of such a community is the remote region of Spiti Valley, India. Nestled 3,800m high among the Indian Himalayas, this region lacks road access seven months of the year due to snow coverage on the high mountainous passes, making access to basic healthcare services, including dental care, a challenge.[4] Historically, this region was isolated from the rest of civilization for the majority of the 20th century.[5] However, through recent globalization and increased access to high sugar foods, this region has seen a dramatic increase in the prevalence of pediatric dental caries.[5] Geographical isolation, combined with a cariogenic diet, makes Spiti Valley a prototypical remote community, ideal for studying the impact of social determinants of health (SDH) on caries formation.

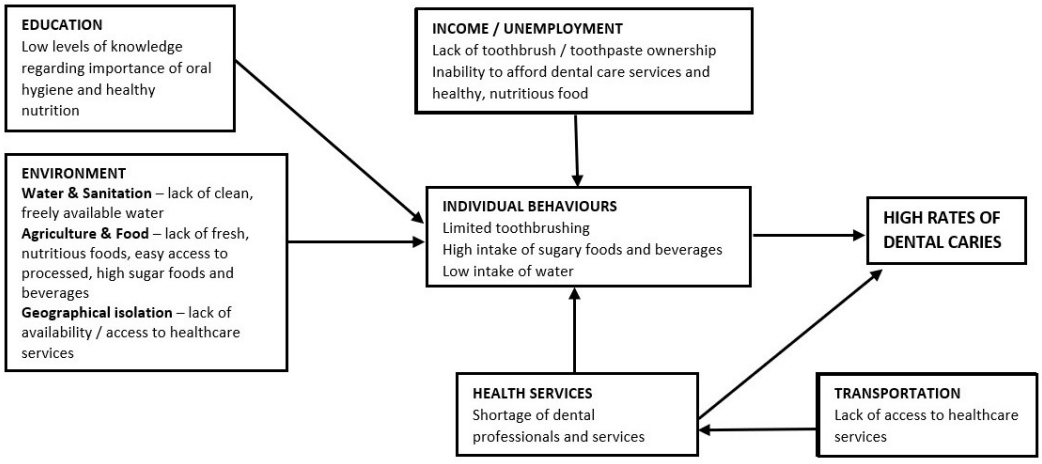

Figure 1 |Social determinants of health that impact dental caries formation.

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Dental caries is a chronic, irreversible condition caused by demineralization of tooth structure by acid-producing bacteria found in dental plaque.[6] It results from a complex interplay between biological (e.g., tooth anatomy, cariogenic bacteria) and SDH.[6] SDH impacting dental caries formation consist of individual behaviors (e.g., toothbrushing, dietary intake) and general socioeconomic, cultural, and

environmental factors (Figure 1).[7] The purpose of this review is 1) to understand the SDH factors impacting dental caries burden in remote communities, using Spiti Valley as an example; 2) to understand the importance of using SDH to inform preventative oral health program (OHP) design, and lastly; 3) to provide best practice guidelines for implementing OHPs in remote communities worldwide.

Methods

For this literature review, a search for English-language articles published between January 2000 to May 2020 describing OHPs in Spiti Valley, India was conducted using MEDLINE and PubMed databases as well as other sources such as periodicals, conference proceedings, reports, and web-based articles. Keywords used included: dental health, oral health, dental caries, dental care, oral hygiene, tooth decay, cavities, social determinants of health, social environment, health services accessibility, Spiti, and Spiti Valley.

To better understand how SDH factors impact OHP design in other remote communities, a second literature search using the same parameters, databases, and keywords (excluding "Spiti" and "Spiti Valley") was conducted.

In both literature searches, articles were included if the OHPs used preventative interventions to address pediatric dental caries in remote communities. Articles were excluded if the study sample included special needs children or if the program lacked preventative interventions.

Results

SDH factors used to inform preventative oral health programs in Spiti Valley, India

The first literature search for articles describing OHPs in Spiti Valley yielded eight results. All article abstracts were screened based on the inclusion and exclusion criteria described in the Methods section. This led to five articles, pertaining to three OHPs, being included in this review (Table 1).[5,8-11] Three of the five articles pertain to outcomes of the same OHP at different time points.[5,8,9]

Over the years, three international teams have implemented OHPs in Spiti Valley schools (Table 1).[5,8-11] In 2006, Medical Checks for Children, a team from Holland, was among the first to assess caries burden among Spiti children.[11] They found that dental caries was the most prevalent pediatric disease and attributed lack of oral hygiene and education as major contributing SDH factors.[11] Starting in 2008, two other teams, the Canadian University of British Columbia Global Health Initiative (UBC GHI),[5,8,9] and the Australian Himalayan Spiti Dental Program (HSDP),[10] have been collaborating to identify other SDH factors impacting caries burden in this community and have implemented OHPs aimed at addressing these factors (Table 2).[5,8-10,12]

Over the years, the UBC GHI team has implemented preventative interventions including 1) school-wide brushing routine; 2) toothbrush storage systems; 3) toothbrush and toothpaste provision; 4) student and staff education.[5,8,9] In addition, they have collaborated with Non-governmental Organizations (NGOs) to install water tanks and handwashing stations.[12] The HSDP team has provided surgical interventions (e.g., tooth fillings and extractions), in addition to preventative strategies such as toothbrush and toothpaste provision, education, and fluoride application.[10] Recent data indicates that these strategies have been successful at promoting daily brushing among students, which increased from 19% in 2017 to 65% in 2018.[5,8]

However, despite these improvements, dental caries burden among Spiti Valley school children remains high and largely unchanged over the past decade: 67% in 2008, 62% in 2017 and 61% in 2018.[5,8,9] Figure 2

Table 1 |Summary of oral health projects in Spiti Valley, India identified in the literature review.[5,8-11]

Year [ref]	International Team	Study location (school, village)	OHP Interventions	Findings
2006[11]	Medical Checks for Children (Holland)	Munselling school, Rangrik	Dental health education	Dental caries was the most common illness among Spiti children. SDH factors identified: poor dental hygiene, lack of education
2008 - present[5,8,9]	University of British Columbia, Faculty of Medicine, Global Health Initiative (UBC GHI) (Canada)	Munselling school, Rangrik	School-wide daily brushing routine, dental health education, toothbrush/paste distribution, toothbrush/paste storage solutions	2008[9] 400 students screened Students with ≥ 1 dental caries – 67%
				2017[5] 486 students screened Students with ≥ 1 dental caries – 62% Daily toothbrushers – 19% Toothbrush ownership – 68%
				2018[8] 530 students screened Students with ≥ 1 dental caries – 61% Daily toothbrushers – 65% Toothbrush ownership – 89%
2008 - present[10]	Himalayan Spiti Dental Program (HSDP) (Australia)	Munselling school, Rangrik Serkong schoo, Tabo	Dental fillings, extractions, topical fluoride, dental health education, toothbrush/paste donation/distribution	In addition to caries prevention interventions, the HSDP team provided the following surgical interventions (data from 2008).

	Munselling school	Serkong school	Total
Fillings	117	35	152
Extractions	178	58	236

OHP - oral health program

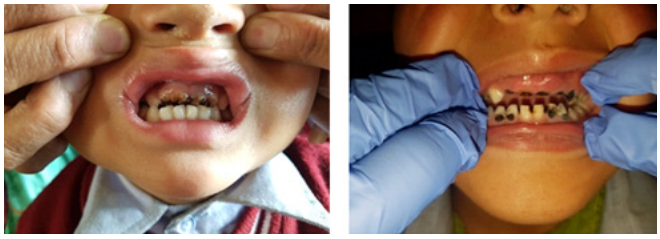

Figure 2 |Rampant dental caries among Spiti Valley school children (2017).[5]

shows examples of rampant pediatric caries from the year 2017.[5] This is largely due to the students' cariogenic diet, a key SDH factor that has yet to be addressed.[8] The majority of Spiti Valley students live in campus dormitories and rely on school-provided meals for sustenance.[8] However, due to limited school funding and lack of local access to nutritious foods, school meals consist mostly of carbohydrates and sweetened tea also known as chai.[8] Furthermore, recent surveys showed that students supplement their school meals with high sugar snacks, purchased from the local convenience store, as often as three and a half days per week.[8]

In summary, the beneficial effects of daily toothbrushing achieved by the Spiti Valley OHP are being overshadowed by the students' cariogenic diet, thereby underscoring the importance of addressing all modifiable SDH factors to affect disease burden. Future efforts must therefore, address factors such as limited school funding and access to nutritious foods that continue to contribute to this region's cariogenic diet.

SDH factors used to inform preventative oral health programs in other remote communities

The second literature search, pertaining to OHPs in other remote communities, yielded 73 results. All 73 abstracts were screened based on the inclusion and exclusion criteria described in the Methods section. This led to five articles, pertaining to four OHPs, being included in this review (Table 3).[13-17]

Analysis of these four OHPs showed that remote communities around the world share many SDH factors identified to be impacting dental caries burden in Spiti Valley.[13-17] These include:

1. Individual behaviours: limited toothbrushing,[13-15] and a high sugar diet;[13-15,17]
2. Limited education regarding oral health and nutrition;[13-15,17]
3. Low income,[11] and low rates of toothbrush and toothpaste ownership;[13-15,17]
4. Limited availability and access to oral healthcare services;[13-17]
5. Environment: geographical isolation,[13-16] limited access to nutritious foods,[17] clean water,[17] and electricity.[17]

Further analysis showed that using these SDH factors to inform OHP design can lead to reduction in a community's caries prevalence.[13,17] This was highlighted in the Macnab et al. study,[13] which took place in the remote First Nations community of Hartley Bay, Canada, and the Dabiri D et al. study,[17] which took place in 15 rural communities in El Salvador. Both studies implemented similar interventions, such as fluoride application,[13,17] education,[13,17] daily school brushing routine,[13] and toothbrush and toothpaste provision.[13,17] Both studies showed an improvement in caries prevalence: 92% to 68% over 3 years in the Canadian study,[13] and 90% to 70% over 2 years in the El Salvador study.[17] Both studies attributed their OHPs success in large part to continued community engagement through regular visits by the OHP teams.[13,7]

While addressing SDH factors is important, it is not without challenges. This was highlighted in the Roberts-Thomson KF[14] and Slade GD et al. study.[15] Thirty remote Australian Indigenous communities were allocated into intervention and control groups, with 15 control communities receiving no interventions and 15 communities receiving preventative interventions every six months.[14,15] Interventions included

Table 2 |Social determinants of health (SDH) contributing to high caries burden among Spiti Valley school children and interventions by UBC GHI and HSDP teams to address these factors.[5,8-10,12]

SDH factors		Interventions (Team)
Individual behaviours	Limited toothbrushing among students	Implementation of a school-wide toothbrushing routine[5,8]
	High intake of sugary foods and beverages	Student education[5,8-10]
Education	Low levels of knowledge regarding the importance of oral hygiene and healthy nutrition	Student education[5,8-10]
Environment	**Geographical isolation:** challenging, mountainous terrain and lack of road access 6-7 months of the year due to snow	Non-modifiable
	Water & sanitation: lack of clean, freely available water	Installation of handwashing stations and water pumps[12]
	Agriculture & food: limited availability of fresh, nutritious foods locally, school meals low in nutritional value, and easy access to high sugar snacks at the local convenience store	
	School environment: majority of students live in dormitories on school grounds, overloading school schedule, loss of toothbrushes	Installation of toothbrush storage solutions[5,8]
Health services	Shortage of dental professionals and services - only one dentist available in the nearby town of Kaza	Dental fillings, extractions, and topical fluoride application[10]
Transportation	Lack of safe, affordable transportation needed to access dental services in Kaza	
Income / Unemployment	Limited school funding for supplies (toothbrushes, toothpaste), nutritious school meals, dental services	Toothbrush/toothpaste donation to school[5,8-10]

Table 3 |Summary of oral health programs in other remote communities identified in the literature revew .[13-17]

Author, year [ref]	Study Design	Study Population	Interventions	SDH Factors
Macnab A et al, 2008[13]	Cross-sectional study	KG to Grade 12 children in the remote First Nations community of Hartley Bay, Canada	School-based daily brushing program, fluoride application, student education, toothbrush/paste provision	Limited toothbrush ownership, toothbrushing, education, availability/access to OHS, high sugar diet, geographical isolation
Roberts-Thomson KF et al, 2010*[14]	Clustered-randomized controlled trial	Children 18-47 months of age in 30 remote Indigenous communities across Australia	Fluoride application, toothbrush/paste provision, dental health education, training primary care providers to be OHP providers	Limited toothbrush ownership, toothbrushing, education, availability/access to OHS, high sugar diet, geographical isolation
Slade GD et al, 2011*[15]	Clustered-randomized controlled trial	Children 18-47 months of age in 30 remote Indigenous communities across Australia	Fluoride application, toothbrush/paste provision, dental health education, training primary care providers to be OHP providers	Limited toothbrush ownership, toothbrushing, education, availability/access to OHS, high sugar diet, geographical isolation
Mathu-Muju KR et al, 2011[16]	Cross-sectional study	Children 5-7 years of age in 320 remote First Nations and Inuit communities across Canada	Fluoride varnish, fissure sealants, oral health counseling, stabilization of active caries with glass ionomer	Geographical isolation, limited availability/access to OHS, feelings of lack of autonomy over one's health care decisions
Dabiri D et al, 2016[17]	Cross-sectional study	Children 0–6 years of age in 15 rural communities in El Salvador	Fluoride application, education, toothbrush/paste provision	Lack of formal education, limited access to OHS, low income, low toothbrush/paste ownership, limited access to nutritious foods, high sugar diet, limited access to clean water and electricity

*Articles pertain to different outcomes of the same study, OHS - oral health services, OHP - oral health programs, SDH - social determinants of health

fluoride application, toothbrush and toothpaste provision, education, and training primary care providers to be OHP providers.[14,15] After two years, the intervention communities had significantly less caries, by an average of 3.0 tooth surfaces, compared to the controls.[15] This was largely attributed to fluoride application, as there was no significant change found in individual toothbrushing and sugar intake behaviours between the groups.[14,15] However, over this period, 89% of children from both groups had developed new caries, indicating that fluoride alone is not sufficient.[15] The authors attributed the OHPs inability to affect individual behaviours to social challenges, such as potential difficulties in the uptake of "European" caries prevention strategies in the context of traditional Indigenous health practices, and lack of local primary care providers' involvement in the OHP due to their heavy workloads and high staff turnover.[14]

Table 4 |Best practice guidelines for designing and implementing preventative oral health programs in remote communities.[5,8-11,13-17]

1	A preventative oral health program design must begin with; • an epidemiological assessment of the community's caries burden, an • a comprehensive assessment of the underlying social determinants of health (SDH)
2	These SDH factors should form the basis of interventions chosen to promote caries prevention. Inability to address any number of these factors can affect the long-term success of the program.
3	The interventions should be chosen in collaboration with the community and must be evidence-based, sustainable, culturally competent, and meet the specific needs of the community. This requires: • Meeting with the community to determine its needs, readiness, and commitment • Empowering the community to feel autonomous over its own oral health care decisions, by emphasizing community ownership of the program, • Allowing the community to make an informed decision on whether or not to participate in the program • Ensuring ongoing community engagement by recruiting and training local community members as dedicated oral health workers, whose purpose is to help support the visiting dental professionals and provide a sustained dental presence between visits • Investing resources to incorporate oral health into the wider context of traditional health practices of the community • Integrating caries prevention into the broader primary healthcare priorities of the community (e.g. incorporating oral health as part of well-child visits with primary care providers and pediatricians).
4	Methods for evaluating and recording intervention outcomes such as caries prevalence, frequency of oral hygiene behaviours, dietary patterns, etc. must be determined at the start of the program.
5	Lastly, the program's effectiveness must be evaluated and a detailed analysis of factors contributing to its successes and shortcomings must be conducted. An ongoing assessment of SDH factors and input from the community are key.

Access to oral healthcare services is an important SDH factor that impacts remote communities. This was the focus of Canada's largest Indigenous caries prevention program, called the Children's Oral Health Initiative (COHI).[16] It began as a pilot project in 41 First Nations and Inuit communities (FN/I) in 2004, and grew to include 320 communities by 2014, representing 55% of all eligible FN/I communities.[16] In 2012, 23,085 children had accessed COHI preventative services.[16] The program's success has been attributed to its innovative model. In addition to employing dental hygienists to provide preventative dental services, it trained a community member, called a COHI aide, to advocate for preventative oral health in the community and provide caries prevention education to children, parents, and expectant mothers. Sustained community engagement through the presence of this COHI aide has enhanced the widespread acceptance and utilization of the COHI program within these remote communities.[16]

Discussion

Best practice guidelines for designing and implementing oral health programs in remote communities

Implementing an OHP, especially in a remote community, is challenging. Given the geographical isolation of these communities, availability and access to oral healthcare services is often limited.[18,19] Therefore, OHPs must focus their efforts on caries prevention.[18,19] Based on the lessons learned from OHP outcomes in Spiti Valley,[5,8-11] and other remote communities,[13-17] a list of best practice guidelines for designing and implementing such programs is provided in Table 4.[5,8-11,13-17]

Conclusion

Pediatric dental caries burden is high in remote communities worldwide. SDH factors, such as low income, limited education, as well as limited availability and access to oral healthcare services, nutritious foods, clean water, and electricity are major contributors. Understanding and addressing these factors is key to the long-term success of OHPs implemented in these communities. In addition, ongoing community engagement is paramount for the program to be sustainable, culturally appropriate, and to meet the specific needs of the community. Investing resources to train community members as dedicated oral health workers and integrating caries prevention into broader healthcare priorities and practices of the community are some of the many ways to ensure the long-term success and sustainability of the program. In remote communities such as Spiti Valley, where the caries burden remains high despite caries prevention strategies, continued efforts are needed to identify and address SDH factors, like cariogenic diet, that continue to contribute towards dental caries formation.

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Conflict of interest

The authors have declared no conflict of interest.

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Rapid induction of buprenorphine/naloxone from methadone using a micro-dosing approach for opioid use disorder treatment in an inpatient setting: A case report

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Abstract

Background and purpose: Opioid agonist therapies such as methadone and buprenorphine/naloxone (BUP/NX, trade name: Suboxone) are essential treatment options for those with opioid use disorder. Markedly different pharmacological properties between the two treatments render the transition from methadone to first-line BUP/NX opioid agonist therapy challenging. Current guidelines recommend complete cessation or tapering of methadone before starting BUP/NX induction to prevent the onset of precipitated withdrawal. However, cessation or tapering of methadone is often poorly tolerated by patients.

Methods: Clinical Case Report

Results: This case describes a patient who was successfully transitioned from methadone to BUP/NX using a rapid five-day micro-dosing induction technique that required no preceding cessation of methadone and caused no clinically significant precipitated withdrawal symptoms during treatment.

Conclusion: This case report presents a novel case which until now, has not been described in the literature and provides an approach to address shortcomings in current BUP/NX induction guidelines.

Introduction/Background

In the United States (US) and Canada, there are ongoing public health crises characterized by elevated rates of drug overdose due primarily to an illicit drug supply contaminated with the synthetic opioid fentanyl and its analogues.[1,2] From 2017 to 2018, the US reported a near 10% increase in the rate of synthetic-opioid-involved deaths from 9.0 to 9.9 per 100,000.[2] In 2018, synthetic-opioid-involved deaths accounted for 67% of the total 46,802 opioid-related overdose deaths in the US.[2] From January 2016 to September 2020, over 19,355 opioid-related deaths occurred in Canada with a 45% observed increase in Canada's opioid-related death rate between 2016 and 2017.[1]

Despite the high mortality rate associated with illicit opioid use, effective treatment options exist that serve to reduce the harms of opioid use for patients.[3] The current first-line opioid agonist treatment (OAT) in Canada includes the partial mu-opioid receptor agonist buprenorphine/naloxone (BUP/NX, trade name: Suboxone) and its alternative, the long-acting full opioid agonist methadone.[4] Of note, buprenorphine exists in formulations such as transdermal and injectable buprenorphine which do not include naloxone.[5] Patients may transition between these treatment options and others for a myriad of reasons including pharmacokinetic interactions, contraindications, and treatment induction procedures.

Current guidelines in North America recommend that for individuals on methadone, BUP/NX induction commences following either a reduction or complete cessation of methadone dosage 24–72 hours prior to BUP/NX induction and a complete cessation of other opioids until the patient is experiencing mild to moderate opioid withdrawal symptoms (per the Clinical Opiate Withdrawal Scale).[6,7] This approach can be time-consuming and the requirements of illicit opioid cessation, methadone dose reduction or cessation, and withdrawal symptoms can be substantial barriers for patients and increase the risk of relapse to illicit opioid use.[8,9] Challenges with BUP/NX induction after methadone treatment result from the differing pharmacokinetics of the two therapies. BUP/NX has a higher affinity than methadone for the mu-opioid receptor and can cause precipitated withdrawal if initiated in the presence of methadone or other opioids.[5] In the face of these challenges, there is little agreement between the published guidelines for the transfer of patients receiving methadone to BUP/NX, and other approaches must be considered.[10] One emergent alternative induction approach uses micro-dosing of BUP/NX.

Micro-dosing BUP/NX is a novel transition approach that circumvents the necessity for patients undergoing BUP/NX induction to abstain from opioid use and/or to present with objective withdrawal.[11] The principle of micro-dosing is the delivery of small doses of BUP/NX over time such that the partial agonist slowly accumulates at the mu-opioid receptor and replaces any bound full agonists like diacetylmorphine, fentanyl, or methadone.[12] This approach was initially described in a single case report in 2010,[13] and has been described in a small number of case reports and case series since then.[12,14–19] These case reports describe inpatient and outpatient BUP/NX inductions to transition from full mu-opioid receptor agonists including, but not limited to, illicit opioids,[13,15,16] methadone,[12,17] and injectable opioid agonist therapies.[14] However, induction by micro-dosing can take extended periods of time to complete, from 7 to 29 days.[17,12]

It is essential to investigate alternative induction strategies for BUP/NX as it is the preferred first-line opioid agonist therapy given its superior safety profile, including lower risk of overdose,[20] ceiling effect at high doses (when not used concurrently with alcohol and benzodiazepines),[21] fewer drug interactions,[22] and no implications for prolongation of the QT-interval (QTc).[4,5]

The following case describes a patient who successfully transitioned from methadone to BUP/NX using a rapid five-day micro-dosing induction technique in an inpatient setting, with no preceding tapering or cessation of methadone and no clinically significant precipitated withdrawal symptoms experienced by the patient. This case report illustrates the value of rapid micro-dosing as a possible induction technique for BUP/NX.

Written informed consent was received by the patient to publish this case exempt from Institutional Review Board (IRB) and ethics

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review per the University of British Columbia policy (4.4.2 Case Reports).[23] This case report adheres to the CARE guidelines for clinical case reporting.[24]

Case

The patient, a 46-year-old woman, was admitted to an urban tertiary care centre in Vancouver, BC, for osteomyelitis and diskitis. Her past medical history was significant for diskitis and osteomyelitis of multiple cervical vertebrae with associated epidural abscesses requiring a surgical intervention and hardware, hepatitis C virus infection, schizophrenia, and polysubstance use. Substance use at admission included approximately 0.1 grams of heroin/fentanyl injected daily, occasional use of intravenous crack cocaine and smoked crystal methamphetamine, and ten cigarettes smoked per day. The patient reported injecting opioids for the past ten years. The patient had previously been on methadone, but not in the past year, and had never been on BUP/NX.

At admission to hospital, the patient elected to initiate treatment for opioid use disorder with OAT methadone starting at 10 mg oral liquid three times a day, morphine oral liquid for pain (10 mg to 30 mg orally every three hours as needed), and nicotine replacement therapy.

The patient was transferred to a second tertiary care centre for surgery after the patient reported bilateral upper back pain resulting in identification of an abscess from C5 to T3 and diskitis of C5, C6, and C7. At this centre, the patient received surgical decompression of C5 to T3 epidural abscess, cervical corpectomy of C5, C6, and C7, instrumentation and fusion from C3 to T3, and was initiated on a twelve-week course of antibiotic therapy for methicillin-susceptible Staphylococcus aureus (MSSA) bacteremia and osteomyelitis. At the time of transfer back to the original admitting hospital, she was receiving methadone (15 mg orally three times a day), gabapentin (400 mg orally three times a day), cloxacillin (2 g intravenously every eight hours), nicotine replacement therapy, loxapine (10 mg orally or intramuscularly daily), and risperidone (37.5 mg intramuscularly weekly).

A consult from the hospital's addiction medicine consult service was requested by the admitting team who had concerns about QTc prolongation from risperidone,[25] a central nervous system depressant, in combination with methadone.[26] Additionally, rifampin was being added to the antibiotic regimen,[27] which further interacts with methadone and reduces methadone concentrations, rendering it challenging to maintain therapeutic dosing levels.[28] BUP/NX was suggested as an appropriate OAT for the patient as it addressed concerns regarding QTc prolongation on methadone and it additionally met the patient's personal desires for increased flexibility for travel and take-home dosing.

The patient was informed about the risk of precipitated withdrawal and consented to a rapid micro-dosing induction. On day one of the induction, while still receiving 15 mg methadone every eight hours, the patient was started on a dose of 0.5 mg of sublingual (SL) BUP/NX with a second dose of 0.5 mg in the evening for a total dose of 1 mg. On day two the BUP/NX dose was increased to 0.5 mg every three hours (for a maximum dose of 2.5 mg in 24 hours) and methadone was discontinued. No methadone taper was conducted. On day three the BUP/NX dose was increased by 0.5-1 mg every three hours (for a maximum dose of 8 mg in 24 hours). On the fourth and final day of the induction, the patient was at a therapeutic dose of 12 mg per day (see Table 1). No clinically significant precipitated withdrawal symptoms were experienced by the patient. The patient was then maintained on this stable dose of BUP/NX for the following two weeks of her admission.

Two weeks after the rapid micro-induction, the patient was discharged to her home on a maintained dose of 12 mg daily of BUP/NX and completed the remaining weeks of her antibiotic regimen with a community transition care team. Once discharged, the patient was followed by a mental health and addictions team in the community.

Table 1 |Dosing schedule for rapid micro-induction

Day	Methadone (mg)		Buprenorphine/Naloxone (mg Buprenorphine)	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
0	15 mg q8h	45 mg	N/A	N/A
1	15 mg q8h	45 mg	0.5 mg q8h	1 mg
2	Discontinued	N/A	0.5 mg q3h	2.5 mg
3	N/A	N/A	1 mg q3h	8 mg
4	N/A	N/A	12 mg daily	12 mg
5	N/A	N/A	12 mg daily	12 mg

*N/A (Not Applicable); q8h (every eight hours); q3h (every three hours)

Discussion

This case report describes a novel BUP/NX rapid micro-dosing induction protocol for a patient with opioid use disorder admitted to hospital transitioned from hospital-initiated methadone to BUP/NX. Rapid micro-dosing is a novel technique that simultaneously bypasses the need for pre-induction opioid cessation and the possibility of precipitating withdrawal while also being compatible with the constraints for efficient inpatient induction, a process challenging to complete with methadone due to its long half-life.[26]

At the time of writing, a small number of case reports describing micro-dosing inductions transitioning from methadone to buprenorphine and BUP/NX have been published in the literature.[12,17,29] Notably, only one small case series from Vancouver, Canada and two case reports have previously described a rapid micro-dosing induction technique.[15,18,29]

One case report describes a 60-year-old man with an opioid use disorder transitioning to BUP/NX after 30 years of methadone treatment.[29] This rapid micro-induction took place over 11 days (which is more typical of a non-rapid micro-dosing induction) in an outpatient setting where the patient started on transdermal buprenorphine and transitioned within that time period to a therapeutic dose of 16 mg sublingual BUP/NX. The patient experienced mild withdrawal after cessation of methadone on day 11 of the induction.[29] In the second case report, Azar et al. report the case of a 16-year-old girl with a severe opioid use disorder admitted to a pediatric hospital interested in starting OAT for the first time.[18] A three-day rapid micro-dosing induction to a dose of 12 mg BUP/NX was used to bridge the patient to a monthly dose of 300 mg injectable extended-release buprenorphine (Sublocade). The patient experienced some withdrawal symptoms but did not show any signs of precipitated withdrawal during the induction.

Recent provincial guidelines from British Columbia, Canada have recommended considering either a micro-dosing or rapid micro-dosing approach to avoid the need for moderate withdrawal and to mitigate the risk of overdose-related morbidity and mortality for people who use drugs during the coronavirus disease 2019 (COVID-19) pandemic.[30] Amidst the pandemic, BUP/NX's superior safety profile and potential for longer-term take-home dosing may also be one means of minimizing risk for people exposed to the risks of an increasingly limited and toxic

drug supply.[31]

Conclusions

This case report presents a novel case with a transition using rapid micro-induction from the long-acting mu-opioid receptor agonist methadone to BUP/NX in an inpatient setting, which until now, had not yet been described in the literature. Furthermore, this case report reinforces the feasibility of rapid micro-dosing as an induction approach in an inpatient setting which addresses limitations of the current guidelines and describes a change in practice that could increase accessibility to BUP/NX.[6,7] Further research on this approach should evaluate the suitability and efficacy of rapid micro-dosing induction in diverse patient populations and continue to develop the evidence base to efficaciously respond to the ongoing opioid crisis in North America.

Conflict of interest

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A mixed presentation of septic pelvic thrombophlebitis: a case report

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Abstract

Background: Septic pelvic thrombophlebitis (SPT) is a rare postpartum complication that is often difficult to diagnose and can be life-threatening. There are two types of clinical presentations of SPT described: ovarian vein thrombosis (OVT) and deep septic pelvic thrombosis (DSPT).

Case: Here we present a case of a 26-year-old woman who presents 13 days postpartum with a mixed picture of OVT and DSPT. She presented to our hospital with fever and abdominal pain with extensive laboratory work-up that did not identify a cause. She was treated with antibiotics and anticoagulation and made a full recovery.

Conclusion: This case highlights the various ways in which SPT can present, complicating the diagnosis. This is of particular importance given that SPT is a predominantly clinical diagnosis.

Introduction

Septic pelvic thrombophlebitis (SPT) is a rare postpartum complication with an incidence of 1 in 9000 spontaneous vaginal deliveries and 1 in 800 cesarean sections.[1,2] According to a multicenter cohort study in 2017, the risk factors for SPT include: peripartum infections, caesarean section, maternal age less than 20 years, non-Hispanic black race, and multiple gestations.[2] Although rare, SPT is often difficult to diagnose and can be life-threatening; progression of disease can lead to septic emboli, pulmonary embolism, shock, and death.[3] The average maternal mortality was reported to be 50% in the early 1900s, 10% in 1951, and 4.4% in 1981.[3] This decrease in mortality is owed mainly to advances in treatment and awareness of clinicians.[3]

There are two clinical syndromes of SPT described: ovarian vein thrombosis (OVT) and deep septic pelvic thrombosis (DSPT).[4] The pathogenesis of the two syndromes are similar: endothelial injury in the intrapartum, venous stasis, and a hypercoagulable state (Virchow's triad) in combination with intrapartum infection leading to thrombosis of pelvic veins.[5] However, the clinical presentation and imaging results are different. OVT classically presents as abdominal pain on the involved side beginning 1–4 days postpartum with fever, leukocytosis, and occasionally a palpable "rope-like" mass extending laterally from the uterus.[6] CT or MRI will often reveal enlargement or filling defect in the ovarian vein on the involved side.[4] DSPT on the other hand, also known as enigmatic fever, is a subacute condition that presents 3 days to 3 weeks postpartum with intermittent fever. Patients can be clinically well between fever episodes.[7] Imaging is less useful in the case of DSPT as it is often difficult to visualize the smaller veins of the pelvis.[4] (Table 1)

Here we describe the case of a 26-year-old woman who presented 13 days postpartum with a mixed picture of OVT and DSPT. She sought medical attention multiple times with nonspecific symptoms, both with and without fever, before presenting to our hospital with fever and abdominal pain. She was treated with broad-spectrum antibiotics for a prolonged duration without resolution. She was ultimately treated for presumptive SPT and made a full recovery. The patient discussed provided written consent to share her case, exempt from Institutional Review Board (IRB) and ethics review per the University of British Columbia policy (4.4.2 Case Reports)

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Table 1 |Comparison of characteristics of OVT and DSPT, the two established presentations of SPT.

	OVT	DSPT
Pathophysiology	Virchow's triad and intraparatum infection	
Timing of onset	1-4 days postpartum	3 days - 3 weeks postpartum
Clinical findings	RLQ abdominal pain Fever Palpable "rope-like" mass	Intermittent fever
Site of thrombosis	Ovarian vein	Deep pelvic vein
Laboratory findings	Mild leukocytosis, blood cultures (in only 35% of cases)	
CT or MRI findings	Enlanged ovarian vein Filling defect in ovarian vein	None
Commonly misdiagnosed as	Endometriosis, appendicitis, ovarian torsion, pelvic abscess, urinary tract infection	

Abbreviations: OVT, ovarian vein thrombosis; DSPT, deep septic pelvic thrombophlebitis; SPT, septic pelvic throbmophlebitis; RLQ, right lower quadrant

Case Report

A 26-year-old gravida 2 para 1 (G2P1) patient presented to our hospital 13 days postpartum from an intrauterine fetal demise at 37 weeks and 5 days gestation. She was previously healthy and had an uncomplicated first pregnancy, which was delivered by elective cesarean section.

She first presented to another facility with the complaint of decreased fetal movements where intrauterine fetal demise was confirmed by ultrasound. She was induced and delivered within 24 hours. Her delivery was complicated by postpartum hemorrhage where she lost 2 litres of blood. In the intrapartum, she became febrile and tachycardic and was treated with metronidazole (Flagyl) and cefazolin (Ancef) for presumed chorioamnionitis. This regimen was later broadened to piperacillin/tazobactam (Tazocin) as her fever persisted. Over the course of this admission, she had a normal echocardiogram and CT Pulmonary Emboli Protocol (CT-PE), and an electrocardiogram (ECG) showing sinus tachycardia. She was discharged on postpartum day 2 when she defervesced. Placental pathology later did not identify any signs of chorioamnionitis, funisitis, or villitis as the source of her

infectious symptoms.

On postpartum day 4, she presented to another facility with complaints of fatigue and palpitations. At the time of her assessment, she was afebrile but had an elevated d-dimer and C-reactive protein. She was treated for presumptive endometritis with piperacillin/tazobactam. She had a repeat ECG and inpatient Holter monitor that again revealed sinus tachycardia. She was ultimately discharged on amoxicillin/clavulanate (Clavulin) and metoprolol (Betaloc).

On postpartum day 13, she presented to our hospital with new onset of right-sided intermittent abdominal pain, back pain, palpitations, and subjective fever. She denied sore throat, cough, nuchal rigidity, shortness of breath, diarrhea, dysuria, vaginal discharge, or calf pain. Physical exam revealed tachycardia, temperature of 38°C, and mild guarding of the right abdomen; cardiopulmonary and pelvic exams were otherwise normal. Her blood analysis revealed a decreased hemoglobin and hematocrit, and an elevated d-dimer. An infectious disease workup was conducted to identify other potential sources of her fever. Urine, vaginal, and blood cultures were all negative. Viral PCR studies were negative for COVID-19, influenza, toxoplasmosis, rubella, and parvovirus B19. Serologic studies did not demonstrate evidence of HIV, syphilis, cryptococcus, brucella, bartonella, coxiella, or tuberculosis. In addition to the previous imaging studies (CT-PE and echocardiogram), she also had a normal chest X-ray and pelvic ultrasound. On postpartum day 13, she received an abdominal/pelvic CT with venous phase contrast, which failed to reveal any thrombosis, distension, or acute abnormalities.

As part of the intrauterine fetal demise workup, an extensive autoimmune panel was performed. This revealed the presence of antinuclear antibodies, including anti-Sjogren's-syndrome-related antigen A and B autoantibodies. All other markers were unremarkable, including negative antiphospholipid antibodies. In addition, her rheumatological review of systems was ultimately negative.

Upon presentation to our hospital on postpartum day 13, she was immediately started on enoxaparin (Lovenox) 1 mg/kg BID, as well as ceftriaxone (Rocephin) and metronidazole (Flagyl). On day 14, she developed a delayed hypersensitivity maculopapular rash, which was believed to be caused by prolonged exposure to penicillins prior to this admission. This rash resolved without treatment over the next several days.

By postpartum day 16, she defervesced and her right abdominal pain resolved. She was ultimately discharged on postpartum day 19 with a prescription for metoprolol (Betaloc) and apixaban (Eliquis) ongoing until 6 weeks postpartum.

Discussion

Traditionally, diagnosis and treatment have been via laparoscopic identification and ligation of the thrombosed vein; however, the diagnosis is now made clinically.[5] While imaging such as CT and MRI can be done to confirm the diagnosis, it cannot be used to rule out SPT due to poor visualization of the smaller vessels.[5] Additionally, blood cultures are negative in greater than 65% of cases and cannot be reliably used as a diagnostic tool or to guide therapy.[5]

The classic clinical picture of DSPT is a subacute, intermittent fever with no identifiable source, that fails to respond to broad-spectrum antibiotics but subsequently improves when anticoagulation is added.[5] The typical timing of onset can be anywhere from 3 days to 3 weeks postpartum.[5] OVT, on the other hand, is an acute presentation, occurring 1 to 4 days postpartum, with fever and abdominal pain.[6] Abdominal pain is localized to the right in 90% of cases due to anatomy: the right ovarian vein is longer and more susceptible to collapse postpartum.[9] The patient in our case presented first with intermittent fever. However, unlike the classical DSPT, she was unwell between the febrile episodes, having presented to the hospital once with fatigue and palpitations. On postpartum day 13, she again presented to the hospital; however, her clinical picture in this presentation resembled OVT, with abdominal pain and fever. Atypically, the onset of her OVT-like symptoms was delayed and did not start in the classic timeframe of 1–4 days postpartum.

The pathophysiology of SPT is described by Virchow's triad. In the postpartum period, all three criteria of Virchow's triad are fulfilled: endothelial injury can occur in the intrapartum from pelvic surgery or uterine infection; venous stasis occurs as a result of pregnancy-induced ovarian vein dilation and low venous pressures postpartum; finally, hypercoagulability is a well-known phenomenon in pregnancy caused by increasing levels of clotting factors.[5,8]

Current treatment involves broad-spectrum antibiotics and anticoagulation, although there is no consensus on an ideal regimen. Antibiotics such as clindamycin, gentamicin, and ampicillin (also known as 'triple therapy') are typically chosen to cover for endometritis and enterococcal pathogens.[5] However, there is insufficient evidence for this regimen and it is mostly used due to the fact that when patients present with SPT, they are already being treated with these agents for presumptive endometritis.[4] Use of anticoagulants is also controversial. A randomized control trial (N=15) showed no difference in recovery between antibiotics alone and antibiotics with anticoagulation.[10] However, there have also been multiple case reports describing SPT that does not respond to antibiotics alone with subsequent response when anticoagulation is added.[4,5,6,9,11]

Conclusion

In conclusion, we described a mixed clinical presentation of SPT following the delivery of a singleton deceased fetus vaginally. A pathological analysis did not identify chorioamnionitis, yet she developed a recurrent fever and later abdominal pain. This case highlights the various ways in which SPT can present. This is of particular importance given that there is often no imaging or laboratory test to rely on in SPT; therefore, it is important to keep SPT on the differential, even in patients who were previously low-risk pregnancies. Although it is an uncommon postpartum complication, SPT is an important consideration in the context of fever in the postpartum period because of its potentially fatal outcome. In this case, the decision to continue prolonged anticoagulation through the end of the puerperal period was based on the rationale that her symptoms only resolved without recurrence once anticoagulation had been added and to prevent further complications from thromboembolic events. Our patient ultimately made a full recovery and is doing well.

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Conflict of Interest

The authors declare no conflicts of interest.

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Gender affirming surgery: The future lies in data

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Abstract

In 1957, a great plastic surgeon wrote on gender-affirming surgery, "The surgeon is concerned with the plastic provision of a functioning organ of reasonable form ... The ethical problem of thus directing gender must, in the first instance, rest with the philosopher."[1] Since then, the philosophers have spoken, and the verdict is out: gender-affirming surgery is shown to alleviate some or all of the stress associated with gender dysphoria.[2] The field of gender-affirming surgery has a rich history of progress, but the field lags due to a lack of high-quality research on surgical techniques and outcomes data.

Commentary

Gender-affirming surgery (GAS) has come a long way since its origins. In the last century, procedures and therapies were developed that significantly improved the lives of those experiencing gender dysphoria. However, there has also been pushback against the field of transgender medicine—from the burning of Magnus Hirschfeld's Institut für Sexualwissenschaft by the Nazi Party in 1933 to the controversial closing of the Johns Hopkins University Gender Identity Clinic in 1979.[3] Looking ahead, it might be tempting to think that the future of GAS lies in technological advances in robotic surgery or biomedical engineering. However, given the social and philosophical barriers this field has faced in past decades, the body of literature on GAS outcomes and satisfaction is sparse.[3] Indeed, it is likely that a more meaningful investment in GAS lies in gathering high-quality outcomes data and increasing access for patients.

Gender dysphoria is defined as psychological distress that results from an incongruence between one's sex assigned at birth and one's gender identity.[4] It is also important to note that gender dysphoria as a psychiatric illness is widely contested.[3] Additionally, only a minority of individuals experiencing gender dysphoria choose to undergo surgical transition.[5] While opponents of GAS tout these procedures as elective, many plastic surgeons consider GAS to be life-saving as suicidal ideation in the transgender community is high.[6,7] For instance, a study from the United Kingdom found that 67% of transitioning people thought about suicide before transition versus only 3% after transition.[7] Timely and effective procedures that minimize negative psychological outcomes are therefore an important element of transgender health care.

Gender affirming operations are varied. Male-to-female (MTF) transition can include lower surgeries such as penectomy, clitoroplasty, labiaplasty, orchiectomy, and vaginoplasty, as well as upper surgeries like breast augmentation and facial feminization [Table 1].[8] Female-to-male (FTM) transition can include total abdominal hysterectomy with bilateral salpingo-oophorectomy, vaginectomy, urethroplasty, metoidioplasty, phalloplasty, and scrotoplasty, as well as double mastectomy and facial masculinization [Table 1].[8] Gender affirming care may also include important non-surgical elements such as hormone therapy, hair removal, voice therapy, and psychosocial support.

Interestingly, GAS is not a modern concept. The Roman Emperor Elagabalus (218–222 CE) is said to have offered vast sums of money to any surgeon who could make them a vagina.[9] In times long before aseptic technique and anesthesia, the ancient Hijra of Southeast Asia, who identified as a third gender, also underwent removal of the penis and testes.[9] However, complete physical transition was restricted by surgical limitations until the early 1900s.

Plastic surgeon Sir Harold Gillies performed the first phalloplasty on a transgender individual. In 1946, Gillies used a 'tubed pedicle' method—in essence, he created a tube of abdominal tissue and migrated it over to the groin in several stages and included a neourethra within the tube.[1] The patient, Michael Dillon, underwent 13 operations over four years before his phalloplasty was considered complete. For Dillon, "The world began to seem worth living in after all."[10] Dillon, however, faced great stigma as a transgender man and eventually sought exile in India as a Buddhist monk. Gillies went on to pioneer many new approaches in plastic surgery, including one of the earliest vaginoplasty methods in 1959 using a skin flap method.[3] There are currently many different methods used for vaginoplasty, and the choice depends on the anatomy and preferences of the patient.[3]

Despite much experimentation building on Gillies' original tubed pedicle phalloplasty method, an ideal surgical approach for phalloplasty in FTM transition has yet to be achieved.[3] The radial free forearm flap—a different approach from Gillies' that involves harvesting a large segment of tissue from the forearm—is often the procedure of choice today.[3] However, this method carries a higher risk of urologic complications than other procedures and leaves a large scar where autologous tissue is sourced, which some individuals find stigmatizing.[3] Likewise, in MTF transition, some vaginoplasty techniques are considered superior to others, but it is impossible to know the best technique without high-quality evidence.[11] Valuable data lies in the areas of surgical methods as well as patient outcomes and satisfaction. It is challenging to make informed choices about life-altering surgery without robust data.

In Canada, the lack of outcomes data has been attributed to inconsistent access, long waitlists, and a limited number of surgeons specializing in GAS.[12] Opportunities for data collection are also lost when patients encounter barriers to GAS and travel internationally for surgery.[12] Furthermore, GAS procedures have historically been carried out in private practice—institutions that lack the infrastructure to generate high-quality research studies.[12] A 2017 study from The University of British Columbia stressed the importance of increasing surgical GAS options and increasing locally available surgeons.[13] Not long after this study was published, two new GAS clinics opened: one in Vancouver and one in Toronto. MacKinnon et al.[12] believe that these centres place Canada in a prime position to establish standardized GAS measurement tools and quality improvement. However, opening these centres does not automatically increase the number of surgeons capable of carrying out complex GAS procedures. There are currently no Canadian data on GAS training among surgical residents, although it is considered a "recommended training experience" in plastic surgery.[14] In the United States, one study showed that fewer plastic surgery residents

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Table 1 | Definitions of various gender affirming procedures. Many surgical techniques exist for each type of procedure. Definitions from PHSA Trans Care BC and Johns Hopkins.[17,18]

Male-to-Female Procedures	
Clitoroplasty	Construction of a neo-clitoris, usually from tissue taken from the dorsal side of the glans penis.
Labiaplasty	Construction of neo-labia from tissue taken from penis and/or scrotum.
Orchiectomy	Removal of the gonads and spermatic cord, with or without removal of scrotal tissue. Scrotal tissue can be used for vaginoplasty if desired.
Penectomy	Removal of the penis.
Vaginoplasty	Construction of a neo-vagina from remaining penile tissue. Ideal characteristics include: sexual sensation, ability to urinate while sitting, ability to engage in penetrative sexual intercourse.
Breast construction	Creation, enlargement or shaping of breasts, including nipples with sensation.
Facial feminization	Can include: Reshaping of the nose; brow or forehead lift; reshaping of the chin, cheek and jaw; tracheal shave (Adam's apple reduction); lip augmentation; hairline restoration and earlobe reduction.
Female-to-Male Procedures	
Hysterectomy with bilateral salpingo-oophorectomy	Removal of the uterus, ovaries, fallopian tubes, cervix.
Vaginectomy	Removal of the vaginal lining and closing of the vagina.
Urethroplasty	Lengthening of the urethra and incorporation into the shaft of the penis.
Metoidioplasty	Construction of a penis by cutting ligaments around the erectile tissue (clitoris) to release it from the pubis and give the shaft more length. Ideal characteristics include: sexual sensation, ability to have erection, ability to urinate while standing.
Phalloplasty	Construction of a penis from an autologous donor tissue site (forearm, thigh, abdomen). May or may not include implant. Ideal characteristics include: sexual sensation, ability to have erection, ability to engage in penetrative sexual intercourse, ability to urinate while standing.
Scrotoplasty	Construction of a scrotum usually from labia, may include testicular implants.
Mastectomy and chest construction	Removal of the breasts, shaping of a contoured male chest, and refinement of the nipple and areola.
Facial masculinization	Can include: forehead lengthening and augmentation; cheek augmentation, reshaping the nose and chin; jaw augmentation; thyroid cartilage enhancement to construct an Adam's apple.

were exposed to lower surgeries than upper and facial surgeries, and only 26% of respondents reported a dedicated clinical experience in GAS.[15] In addition to increasing the number of surgeons offering GAS, improving knowledge and understanding of transgender medicine among primary care providers may lower barriers to accessing GAS.[16]

One hundred years ago, transgender medicine and GAS was a nascent field. Huge strides have been made since, despite significant challenges. Looking to the future, the greatest progress in GAS will likely come from coordinated research efforts, in which Canada may play an important role. Likewise, improvements will be made by increasing access to care through streamlined assessment and referral systems, training additional GAS-qualified surgeons, and educating primary care providers.

Conflict of interest

The author has declared no conflict of interest.

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An interview with Dr. Prior: progesterone and the future of women's health research

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Abstract

Women's health research and education covers a wide variety of health concerns and often estrogen is the focus in understanding and treating these conditions. Progesterone, however, plays an essential and often underrepresented role in the complex system of women's reproductive health. In this article, we learn about progesterone from Dr. Prior, an international expert in the endocrinology of women's reproduction whose lifelong research has helped us better understand the role of progesterone for women and the exciting ways it can help women in clinical practice.

Dr. Prior is an internationally celebrated endocrinologist and women's reproductive health researcher whose work has helped countless women worldwide. In 2019, she was the recipient of MSFHR's Aubrey J. Tingle Prize for her inaugural work and has been honoured by Women's Health Research Institute (WHRI) for knowledge translation. Importantly, she is the founder and scientific director of the Centre for Menstrual Cycle and Ovulation Research (CeMCOR), the only research center in the world dedicated to studying menstrual cycles and ovulation. Some of Dr. Prior's most significant contributions focus on demonstrating the importance of progesterone in physiology and its clinical significance in perimenopausal symptoms and bone health.

She recently published a must-read article titled: *Women's Reproductive System as Balanced Estradiol and Progesterone Actions- A revolutionary, paradigm-shifting concept in women's health.*[1] This review illustrates the importance of balance between estradiol and progesterone in womens' reproductive systems. Dr. Prior explains that there exists a cultural and scientific emphasis on estrogen as the women's reproductive hormone (for which the article offers several intriguing historical explanations). This has led to incomplete or inaccurate representation of menstrual cycle physiology in the literature.[2] The article explores the collaboration between estradiol and progesterone; estradiol promotes growth and proliferation whereas progesterone inhibits proliferation and supports cellular differentiation and maturation. These complementary actions have significant implications, not only for reproductive health but for cardiovascular, neurological, and bone health as well. It is now known that even in normally menstruating women, there is a high prevalence of subclinical ovulatory disturbances with shortened or absent progesterone production.[3] This emphasizes the need for further understanding of the role of progesterone in women's reproduction and general health.

In this interview, I had the pleasure of speaking to Dr. Prior about why she believes more appreciation for and research into understanding progesterone can revolutionize women's health.

Tell us about your recent article, "Women's Reproductive System as Balanced Estradiol and Progesterone Actions" in Drug Discovery Today: Disease Models. What inspired you to publish this article?

I was invited to be an editor for a special issue of this journal. It was a chance to emphasize that to better understand women's general and reproductive health, we need to start viewing estrogen and progesterone as key partners in a complex system. I hope that anyone with a scientific background would find it interesting from a historical and conceptual point of view. They can also learn about the crucial interplay between estrogen and progesterone in cells, cycles, and in women's lifelong health.

Tell us more about the role of progesterone and why it deserves more recognition in our understanding of women's reproductive health.

Estradiol (the active form of estrogen in the menstrual cycle) and progesterone are linked in a complex interplay within the menstrual cycle. Generally speaking, at the cellular level, estradiol causes growth and proliferation, whereas progesterone stimulates maturation while inhibiting proliferation.[4] This has implications for reproductive tissues but also for ***every*** tissue—e.g., bone, brain, heart, etc.

However, ovulation, and thus progesterone production, is silent within regular cycles. Subclinical ovulatory disturbances are clinically normal cycles in which ovulation does not occur or the luteal length is too short and progesterone insufficient. They are common in normally menstruating women (over a third of cycles in a population-based Norwegian study)[3] and are almost universal in adolescence or perimenopause. Evidence suggests that a higher than median experience of subclinical ovulatory disturbances during reproductive life are associated with increased risk for osteoporosis, heart attacks, breast and endometrial cancers. We do not fully understand the link between subclinical ovulatory disturbances and long-term reproductive and general health so further research is needed in this area. CeMCOR was the first to discover that silent ovulatory disturbances are associated with bone loss.[5]

Tell us more about progesterone in relation to bone loss.

Adult bone remodeling has two parts: estrogen decreases bone resorption in a rapid process; progesterone increases bone formation in a slower process.[6] Since the normal downward menstrual cycle swings of estrogen increase bone resorption, women need both to prevent bone loss and likely fractures.[7,8] In the article, I explore recent evidence that shows progesterone therapy is associated with gain in bone mineral density by increasing bone formation and it may be beneficial in conjunction with standard antiresorptive osteoporosis therapy.

So how can we better study the role of progesterone in women's overall health?

The first step is to be able to document the presence or absence of progesterone in menstrual cycles. Current methods of measuring ovulation, such as the Quantitative Basal Temperature© are tedious and few women will do them. I hope we can develop an inexpensive monthly

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home test that assesses progesterone's action with sensitivity to detect differences between normal ovulatory and disturbed ovulation cycles. This will allow us to obtain large-scale prospective epidemiologic data on the association of subclinical ovulatory disturbances with later life osteoporotic fractures, heart attacks, breast, and endometrial cancers.

You have shown in randomized controlled trials that progesterone or progestins (acting through the progesterone receptor) are equivalent to estrogen for hot flushes with no difference in short-term side effects.[9,10] How has this translated into your clinical practice?

When I knew the data made sense, was without harm, and could help my patients, I adopted it. Perimenopause can be a very challenging time in many women's lives and many are willing to try new therapies. In my clinical and personal experience, progesterone effectively treats night sweats and sleep problems. Many clinicians still don't know that it's an option. Unfortunately, our CIHR-funded, large perimenopausal VMS RCT of progesterone versus placebo was rejected by all major medical journals without peer review although we are still seeking its peer reviewed publication. Also, oral micronized progesterone (even as a generic drug) has been allowed to become prohibitively expensive in Canada.

How can we, as a community of learners, advocate for more menstrual cycle research?

Sometimes there is a perception in medical education that women's reproductive health is difficult to understand and separate from "general health." We need to start teaching accurate menstrual physiology and considering the menstrual cycle for its contribution to overall health not just to pregnancy. Based on current evidence, a normally ovulatory cycle or its disturbances are likely to have systemic effects. As such, ovulatory menstrual cycles are of key importance for women's lifelong health.

Conflict of interest

The authors have declared no conflict of interest.

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Biological hurdles to pancreatic islet transplantation: where are we at, and where are we going?

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Abstract

Pancreatic islet transplantation has garnered increasing interest over the last two decades due to its promise in treating type 1 diabetes mellitus (T1D), an autoimmune condition that targets and destroys insulin-producing β-cells, which are necessary for the adequate regulation of blood glucose levels. Despite its promise, many obstacles still stand in its way before it can finally be used as a curative therapy for T1D, ranging from donor paucity to the need for immunosuppression. Nonetheless, recent advances in regenerative medicine and xenotransplantation may be a solution to these biological hurdles, owing to their potential as sources of long-lasting β-cells. This commentary aims to discuss some of the various biological hurdles preventing the widespread application of human pancreatic islet (HPI) transplantation, and the various research efforts attempting to address these issues.

Introduction

It has been more than 20 years since Shapiro and colleagues instilled a new sense of hope for those living with type 1 diabetes (T1D) after they reported their findings on a novel islet transplantation technique known as the 'Edmonton Protocol'.[1] In this study, seven patients with T1D were reported to become normoglycemic and insulin-independent after just two or three intraportal implantations of human pancreatic islets (HPIs) and continuous immunosuppression.[1] However, pessimistic views about the Edmonton Protocol settled in quickly once an international trial reported that 76% of the patients had become insulin-dependent again after two years,[2] owing to progressive islet failure and the loss of insulin-secreting β-cells.[3] This innovative technique offers the prospect of reasonable glycemic control without significant surgical risk, but what is currently preventing its widespread clinical application? To address this question, this commentary aims to discuss some of the significant biological hurdles that limit the field of islet transplantation and the ongoing research efforts on various fronts to overcome them.

Biological Hurdles Limiting Islet Transplantation

The Need for Immunosuppression

The autoimmune pathogenesis of T1D presents a very unique challenge to pancreatic islet transplantation. In healthy individuals, insulin-secreting β-cells comprise a cluster of cells known as 'pancreatic islets', which are crucial in the functioning of the endocrine pancreas and the regulation of plasma glucose levels.[4] In those with T1D, β-cell destruction occurs when autoreactive T-lymphocytes recognize β-cell antigens such as insulin and glutamic acid decarboxylase 65 (GAD65),[5,6] with expression of the latter antigen being relatively high in human β-cells.[7] Although autoimmunity against GAD65 has been implicated in T1D pathogenesis, the role and function of GAD65 in normal β-cell physiology is not fully understood.[8] Therefore, the presence of autoreactive T-lymphocytes presents a significant challenge, as the introduction of allogeneic islet grafts can induce a primed immunological attack against transplanted islets,[9] resulting in islet graft failure and β-cell destruction.[10] To suppress this alloimmune response, the Edmonton Protocol involves a combination of T-cell depleting induction therapy (e.g., anti-thymocyte globulin), anti-inflammatory therapy (e.g., anti-TNF, and anti-interleukin 2 receptor antagonist), and maintenance therapy (tacrolimus and mycophenolic acid).[11-15] However, optimization of maintenance therapy (which is used to prevent graft rejection in the long term) poses a significant challenge, as various studies have observed β-cell toxicity and diabetogenicity associated with agents such as tacrolimus,[16, 17] and a host of other side effects such as hypertension, nephrotoxicity and tremors.[14] Given that islet transplantation in some cases is considered a life-enhancing rather than life-saving therapy,[18] these effects are of particular concern as chronic use can result in significant morbidity. However, others may argue that the benefits of islet transplantation far outweigh the drawbacks of immunosuppression, as one of the biggest advantages of islet transplantation is the reduction of severe hypoglycemia and hypoglycemia unawareness associated with T1D,[19] which can potentially lead to death.[20]

Donor Paucity

Despite the promise of islet transplantation, donor paucity remains one of the greatest logistical hurdles hindering the widespread clinical application of islet transplantation.[14] Regardless of how islets are transplanted into the recipient (i.e., within the pancreas for a whole-organ graft or an isolated islet preparation), the source must be from a brain-dead donor, which limits the number of potential islets available for transplantation.[14] Furthermore, islet isolation techniques successfully yield preparations with the appropriate number and quality only about 50% of the time.[14] Combined with the expertise and equipment required in islet preparation and the limited procedural availability of islet transplantation, the critical shortage of islets remain bottlenecks in the widespread clinical application of the therapy.[14]

Biological Hurdles Limiting Islet Transplantation

Advancements in Immunosuppression

Although the need for long-term immunosuppression is a major hurdle preventing the widespread clinical application of islet transplantation, improvements in immunosuppression regimens have yielded five year insulin independence rates greater than 50%.[15] One notable example includes results from the Minnesota group in 2012,[21] which achieved five year insulin independence rates of 70% through the use of T lymphocyte-depleting anti-CD3 monoclonal antibodies and etanercept, a tumour necrosis factor-alpha inhibitor. This is in comparison to the original Edmonton Protocol, which demonstrated a two year insulin-independence rate of only 31% (for those that reached the primary endpoint of insulin independence with adequate glycemic control one year post-transplant).[2]

Genetically Engineered Stem Cells

One of the main areas of active research to address donor scarcity and the adverse effects of immunosuppression is through the implantation

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of genetically engineered human embryonic stem cells (hESCs) as potentially unlimited sources of insulin-producing cells.[22] Previously, various efforts to direct hESCs down the β-cell development pathway only yielded polyhormonal (insulin-, glucagon-, and somatostatin-secreting) cells.[23-25] However, researchers such as Rezania and colleagues have now developed multistep protocols in mouse models that differentiate hESCs into pancreatic progenitor cells capable of maturation in vivo into insulin-secreting β-like cells.[26] Furthermore, in vivo mice studies have shown that these pancreatic progenitor cells are glucose-responsive,[27] and have the potential to further differentiate into functional pancreatic islets capable of reversing diabetes in immunodeficient mice models.[25, 26] Despite the promise of stem cell therapy, one limitation associated with this technique is the tumorigenic potential of pluripotent stem cells when introduced in vivo, especially in individuals that are immunocompromised.[27] However, clinical trials of hESC-based therapies are currently underway, which involve the use of implants containing hESC-derived pancreatic progenitor cells encapsulated by an immune protecting device, minimizing chances of cell escape and/or immune rejection.[28, 29]

Xenotransplantation

Xenografts of pancreatic islets (such as those originating from pigs as islet donors) have also garnered increasing interest in recent years, mainly due to the paucity of HPI donors available for clinical transplantation and limited procedural availability of islet preparation.[30] Neonatal porcine islets have shown particular promise, as not only are they quickly isolated and resistant to hypoxia and hyperglycemia, but they can also expand β-cell mass during transplantation.[31-33] Furthermore, a limited number of case reports have also demonstrated that xenotransplantation of porcine islets into diabetic humans can improve glycemic control.[34] Although xenografts show great promise, the main concern that limits the use of porcine tissues for islet transplantation is that humans possess high antibody titers against galactose α (1,3) galactose, a residue present in high amounts on porcine cells, and are capable of producing a hyper-acute rejection response.[14] However, it is worth noting that generating transgenic pigs lacking the (1,3)-galactosyltransferase gene (and thus the galactose α (1,3) galactose antigen) could be a possibility, such that this hyper-acute rejection can be avoided.[35]

Conclusion

In conclusion, the field of islet transplantation has produced a remarkable amount of research output and innovation in the past two decades, ever since the precedent-setting Edmonton Protocol was introduced. The Edmonton Protocol ignited a new sense of hope in T1D patients longing for a cure to put an end to their ailment. However, despite its promise, many limitations pose a challenge to its widespread clinical application, ranging from the limited supply of donor tissue to the requirement of immunosuppression. Yet, with advancements in immunosuppression regimens and emerging research in stem cell engineering and xenotransplantation, a potential cure may indeed be on the horizon.

Conflict of interest

The authors have declared no conflict of interest.

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New health-focused smartwatches represent a possible paradigm shift for disease screening, but at what cost?

Ryan Chow[1]

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Abstract

Smartwatches, like the Apple Watch, are a class of wearable devices that are growing in popularity. These devices possess sensors capable of collecting physiologic measurements like heart rate/rhythm data, electrocardiogram (ECG) tracings, and oxygen saturation levels. Industry-sponsored research is currently being conducted to investigate the possibility of smartwatches as disease-screening tools. However, the research methods and pervasiveness of these devices may result in an undue burden on the medical system, such as increasing the rate of false positive screening of relatively rare diseases. The purpose of this commentary is to summarize the technologic benefits of these devices whilst also drawing attention to the potential pitfalls of current commercially-driven research.

Introduction

In the fall of 2020, Apple released the 6th iteration of their line of smartwatches, appropriately named the Apple Watch 6. In addition to having a faster processor, a brighter screen, and a wider assortment of eye-catching colours, the Apple Watch 6's keynote feature was its new blood oxygen monitor. After placing the watch snugly on your wrist and remaining still for fifteen seconds, you receive a brief haptic signal from the watch, which reports your arterial oxygen saturation (SpO2) akin to a medical pulse oximeter. The Apple Watch's incorporation of a blood oxygen sensor could be regarded as especially convenient during the ongoing COVID-19 pandemic, as pulse oximetry has been reported to have situational utility in detecting silent hypoxemia, which is characteristic of some cases of pneumonia.[1] However, whether or not the Apple Watch is effective at detecting silent hypoxemia remains to be seen.

The purposes of the first smartwatches were once to deliver notifications, count your steps, and, of course, tell the time. However, technology companies are now touting their devices as health-focused products that can alert you if they detect potential signs of disease. Wearable technology is clearly marking a turning point in the landscape of consumer healthcare, allowing for easier snapshots of physiologic data. However, as current and future medical professionals, we must be wary of the potential implications these devices may have for our practice. This commentary will outline potential benefits and consequences of smartwatches as disease screening tools.

Advances in technology and research methods

As smartwatch technology continues to improve, it is also forecasted that the market for wearable technology will grow by 35.48 billion USD by 2024.[2] The most commonly purchased smartwatches from companies such as Apple, Samsung, Garmin, Fitbit, and Huawei are equipped with sensors like accelerometers to capture activity/motion, Global Positioning System (GPS) chips to track location, electrodes to record electrocardiograms (ECGs), and photoplethysmography sensors to record heart rate and the aforementioned SpO2.[3] The Apple Watch has been the highest grossing smartwatch on the market, commanding 36–40% of all smartwatch sales in the past four years.[4] This is likely due to its fast processor, intuitive user interface, and inherent compatibility with other devices in the Apple ecosystem. As a result of its device's multifunctionality and growing popularity, Apple has been especially engaged in sponsoring medical research involving its smartwatches. The largest study conducted to date has been the Apple Heart Study, a virtual study with 419,297 participants that evaluated the Apple Watch's optical heart rate monitor at detecting atrial fibrillation (AF).[5] The study was regarded as a success, with the authors finding that the device's heart rate monitor is able to detect AF with a high positive predictive value (0.84). Pragmatically, the study also demonstrated the ease and value of recruiting a large number of participants simply by reaching out to owners of an Apple Watch. In Apple's most recent keynote presentation of the Apple Watch 6, they announced plans to conduct three additional large-scale studies to investigate how biometrics from its smartwatch can help manage asthma, heart failure, and respiratory infections including COVID-19.

The burden of pervasive smartwatch screening

An ideal tool to screen disease must 1) be able to catch a disease early 2) be safe 3) be cost-effective 4) be widely available, and 5) lead to improved health outcomes.[6] The traditional implementation of a disease-screening method into clinical practice typically includes extensive scientific research, peer-revision, and academic publication before incorporation into existing practice guidelines for clinicians to utilize and relay to their patients. However, the implementation of smartwatches thus far (especially the Apple Watch) as potential disease-screening tools has instead taken a different methodology where industry has released a screening tool directly to patients/consumers. These individuals then approach clinicians for evaluation of these smartwatch-derived assessments, which eventually spur the need for scientific research (Figure 1). In a critique of the Apple Heart Study in Nature Reviews Cardiology, the author outlines how this mass industry-to-consumer research method could increase the rates of unnecessary screening and consequent false positives, especially for relatively low-prevalence diseases like AF.[7] Higher rates of false positives would place unnecessary anxiety on consumers and could potentially also result in iatrogenic harm from unnecessary treatment (e.g., bleeding risk from anticoagulation therapy for AF). As smartwatch sales grow, this dilemma will be further exacerbated. No study to date has conducted a high-powered risk-benefit analysis of consumer smartwatches as disease screening tools, and multiple other studies have questioned the reliability and false positive rates delivered by the Apple Watch.[8–10] Even if smartwatches were hypothetically highly efficacious at screening for disease, it is ultimately up to the clinician to synthesize this information and take action. However, at this time, there are no management guidelines for clinicians given a patient's abnormal heart rate, oxygen saturation, or ECG biometrics derived from a commercial smartwatch. This consequently leaves primary care

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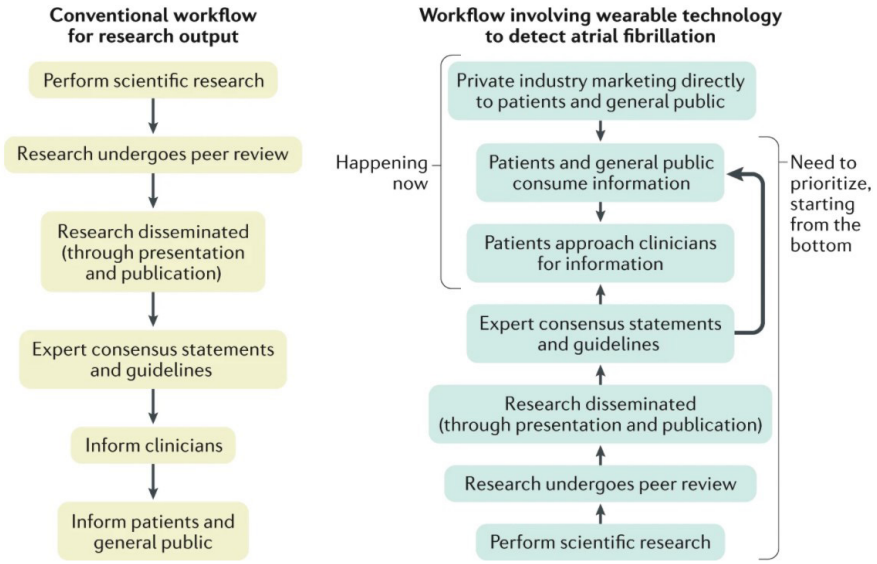

Figure 1 | Conventional workflow for implementation of a screening tool versus the current workflow for the implementation of Atrial Fibrillation screening using the Apple Watch. Adapted from 'Marcus GM. The Apple Watch can detect atrial fibrillation: so what now? Nat Rev Cardiol. 2020;17(3):135–6.'

physicians unable to make informed decisions for their patients, possibly causing anxiety for both physicians and patients.

Conclusion

Deep in the latest Apple Watch user agreement lies the statement, the "Apple Watch is not a medical device and should not be used as a substitute for professional medical judgment." While this may protect Apple from litigation, it does not protect patients from misinterpretation of results and the healthcare system from the burden of overdiagnosis. The Apple Watch provides a tantalizing research opportunity for investigators due to its booming popularity and multitude of sensors. However, more elucidation into the nuances of their disease screening capabilities is required before smartwatches see the light of day in routine clinical practice.

Conflict of interest

The authors have declared no conflict of interest.

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A palliative approach to care: lack of practice standards in sharing goals of care conversations

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Abstract

As Canadians continue to live longer and acquire multiple comorbidities, it is more crucial to integrate palliative care services throughout the illness trajectory and across care settings. This has been further underscored by the COVID-19 pandemic, which has expediated the need for goals of care (GOC) conversations and advance care planning due to illness severity and mortality in vulnerable populations. Here, we comment on the qualitative results of a recent quality improvement project investigating the current state of documentation and workflow practice standards for GOC in the Vancouver Coastal Health Authority and propose key opportunities for improvement.

Introduction

Advanced Care Directives in Palliative Care

Over the last 50 years, life expectancy has steadily increased in Canada leading to a shift in illness trajectory from acute to chronic with multiple co-morbidities.[1] This shift has allowed for individuals to become more aware of their changing health status and establish an Advanced Care Plan (ACP) to communicate their end-of-life care goals. Without an ACP, there is a real risk that patients will undergo interventions or care that is contrary to their beliefs, values, and wishes.[2,3]

Transitions of Care for Patients Receiving Palliative Care

As the illness trajectory of patients with life-limiting conditions progresses, the number of providers in the care team typically increases significantly. With this increase, it is important to find ways to ensure patient wishes are upheld and documented information regarding goals of care (GOC) are effectively shared. However, the number of different electronic medical records (EMRs) used in BC has created challenges in information sharing as patients move across the continuum of care settings; for example, between community, acute, and long-term care (LTC) facilities.[4] Without access to documented GOC, both families and caregivers have limited ability to uphold patient autonomy. Medical professionals are in a unique position to engage in GOC conversations at various transition points, but it has been previously shown that in BC, both the reluctance to document GOC and the complexity of discharge planning have contributed to discordance between patient preference and medical interventions received.[5-7] It is imperative to identify workflow standards that facilitate the sharing of patient plans, so that new providers involved in care have a clear direction about the patient's wishes. The aim of this quality improvement project was to identify gaps in the flow of GOC information from health care providers in one care setting to another and to work with stakeholders to generate improvement ideas to address those gaps.

Methods

Stakeholder Interviews: To gain a better understanding of the gaps in information dissemination, the Regional Palliative Approach to Care Education (RPACE) Team identified key stakeholders involved in delivery of palliative care, including leadership, point-of-care staff, and VCH policy makers in the community, acute, and LTC environments. Key informant sampling was utilized to identify interviewees with an intimate working knowledge of end-of-life care across all settings. Between June and August 2020, we conducted over 50 semi-structured stakeholder interviews, either in-person or over video-based conference calls. Each interview included questions pertaining to the current workflow and responsibilities of each individual to obtain and document GOC, as well as barriers that impede this system.

Data Extraction and Visual Representation: Using the thematic analyses process as outlined by Braun and Clarke, we identified and analyzed patterns that emerged from the stakeholder interviews.[8] This allowed us to create current state maps that model the present practices of documentation flow at care team transition points. In the current state maps, two key areas that we focused on information extraction were:

1. How GOC conversations are conducted and documented in each care setting
2. How documentation is shared between care settings and providers

Finally, we used the Institute for Healthcare Improvement's model for process mapping to explore the potential cause and effect relationship between gaps identified through stakeholder interviews (cause) and poor documentation sharing (effect). This relationship is pictorially presented as an Ishikawa or "fishbone" diagram (Figure 1.)[9]

Results

Current State Mapping: Our general findings from stakeholder interviews are summarized in Figure 2. In the acute care settings, we most frequently heard reports from front-line staff regarding the lack of a standard workflow for initiating and documenting GOC conversations. If documented at all, GOC were frequently hidden within patient progress notes and not easily accessible. Compounding these challenges, workflows and responsibilities were highly variable between hospitals, and even between units. Not surprisingly, unit culture and the perceived hierarchy had a major impact on which care providers engaged in GOC conversations. There was consistently a lack of information sharing both at patient admission and discharge. On admission, clinicians lack access to workflow standards to obtain previously documented GOC from community providers. Additionally, the lack of a common site in admission chart packs to document GOC meant that there was no prompt to initiate a conversation on admission. On discharge, community and LTC providers are often left in the dark regarding what conversations occurred during in-patient stay and often are forced to initiate GOC conversations from scratch in the community. Together, these pose a significant barrier to maintain GOC continuity. A more comprehensive outline of all identified gaps is shown in the fishbone diagram in Figure 2.

Opportunities for Improvement (OFI): Based on the results

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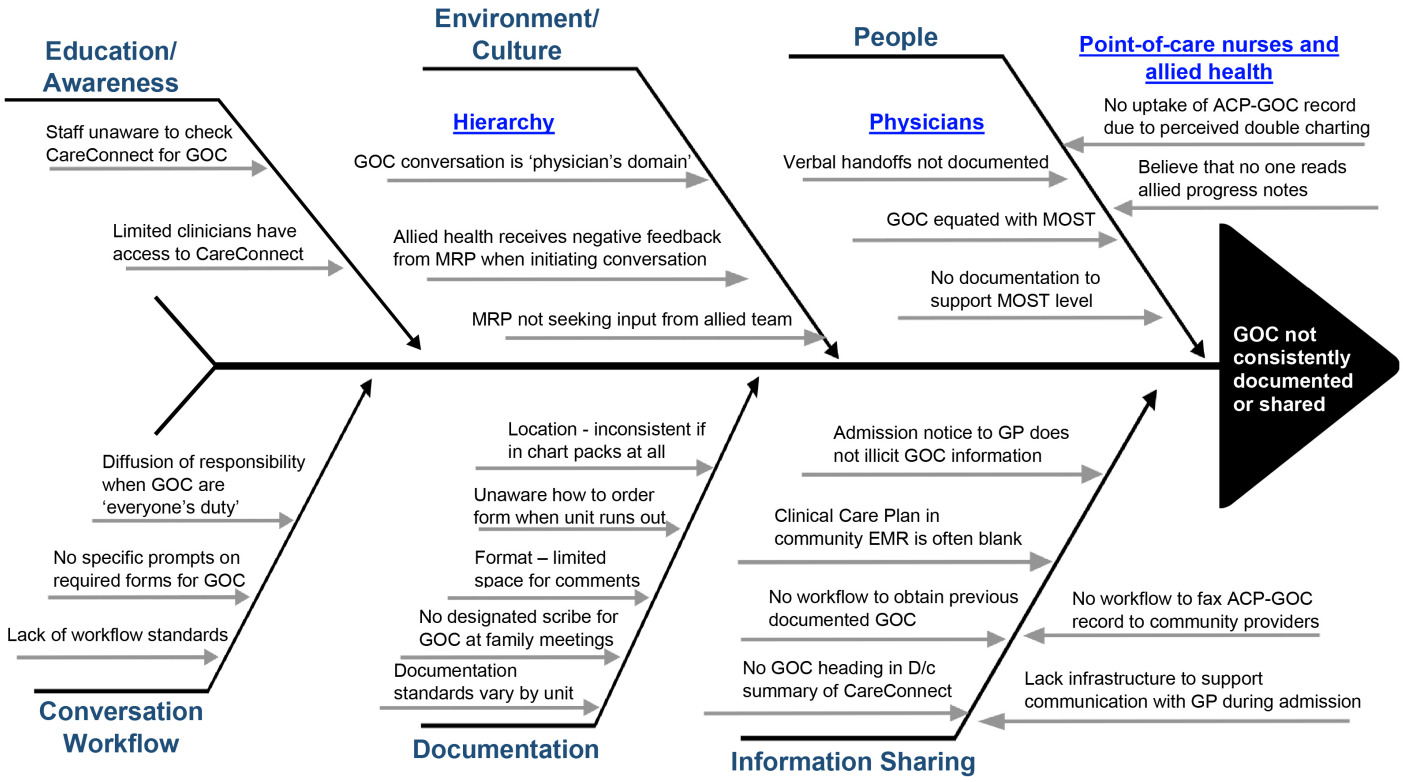

Figure 1 | Ishikawa fishbone diagram identifying all identified gaps contributing to inconsistent documentation and sharing of GOC across care settings. The problem statement (cause) is identified at the 'head' of the fishbone (far right). The major categories of causes of the problem are identified in dark blue: Education/Awareness, Environment/Culture, People, Conversation Workflow, Documentation, and Information Sharing. All identified causes are identified as branches from the appropriate category. GOC, goals of care; MRP, most responsible physician; ACP-GOC, Advanced Care Plan Goals of Care Discussion Record; EMR, electronic medical record; MOST, Medical Orders and Scope of Treatment; D/c, discharge

of our current state map, we have identified key OFIs to improve documentation and continuity. To expedite change, we will highlight improvement areas that are relatively more accessible with fewer barriers to implement.

Regarding documentation, the key OFIs identified are (A) to reinforce and educate providers on the importance of documenting GOC in a single, consistent site within the patient chart and ensure that this information is uploaded to CareConnect (the province's secure, view-only Electronic Health Record that is widely used within six Health Authorities) and thus accessible to clinicians across sites;[10] (B) to include the ACP form on all admissions chart packs alongside pre-existing forms that document the patient's code status;[11] (C) provide families with ACP worksheets upon admission to initiate serious illness conversations.[12] Fortunately, the aforementioned OFIs have already been implemented; however, this clearly underscores the lack of consistency in best practice and the importance of enhanced and consistent provider education. More challenging to modify is the aspect of continuity; we must look to each unit to establish a delineated workflow to check for previously documented GOC on admission (whether in previous patient charts or on CareConnect) and share newly documented discussions with community clinicians upon discharge. This is a key gap that currently falls out of the scope of practice for point-of-care nurses and unit staff that must be addressed in the role descriptions for each unit.

Discussions and Future Directions

As physicians, our mission is to provide the best quality care of to our patients. By engaging in conversation about end-of-life care goals, we can establish a sense of what matters most to each individual and subsequently provide care that aligns with their wishes. This iterative discussion will ultimately better prepare patients and their families for what lies ahead in their illness trajectory.

With support from the BC Patient Safety & Quality Council, we set out to identify how GOC conversations are documented and shared between care settings and providers. In general, our findings suggest that there is very little standard workflow for discussing, documenting, or sharing GOC. This is compounded by information systems that exist on

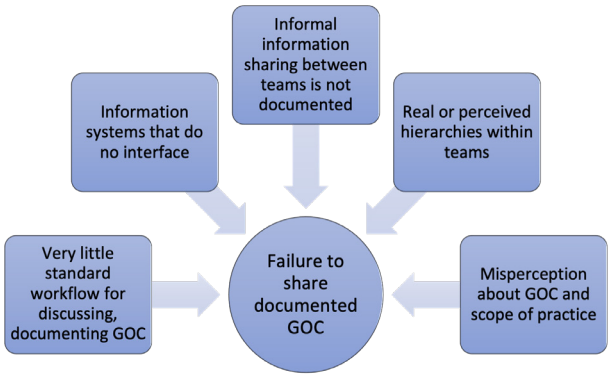

Figure 2 |Key issues raised in stakeholder interviews contributing to failure in sharing documented goals of care.

multiple platforms (paper, electronic, and verbal handoffs) and EMRs that do not interface with one another. To address these challenges, we have identified key OFIs to improve documentation and continuity of GOC conversations.

Importantly, we have taken the first step in the path to improvement to make GOC a priority. As resources permit, we will test ideas for change and measure our improvement in accordance with the Institute for Healthcare Improvement's Plan-Do-Study-Act change cycles.

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Vaccination fascination: exploring unintended consequences of sharing COVID-19 vaccination status on social media

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Abstract

During the introduction of the SARS-CoV-2 vaccine to Canada, social media platforms saw an influx of healthcare professionals sharing their vaccination status with family, friends, and community. This trend, intended to promote vaccine uptake and reduce hesitancy among the broader public, may have the potential to precipitate unintended consequences as immunization rollout continues. This commentary seeks to discuss these potential consequences drawing on past research of healthcare professionals' social media use, the impact of social media upon the COVID-19 pandemic, and vaccination programming.

In December of 2020, social media feeds began to increasingly feature photos of bare deltoids, framed by rolled sleeves, sporting new band-aids. Captions signalled these arms belonged to healthcare professionals receiving the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine. In the midst of an extremely difficult time to work in the healthcare field, these social media posts have become a collective public declaration of hope, gratitude, and happiness. This movement to share vaccination status, which involves posting a picture or caption revealing receipt of the SARS-CoV-2 vaccination on social media, also marks what an exceptional technological advancement the vaccine is for the medical community.[1]

Sharing one's vaccination status on social media likely originated as a trend to promote public SARS-CoV-2 vaccine uptake and reduce hesitancy.[2] Early in the novel COVID-19 pandemic, even before a vaccine had been created, false rumours spread rampantly across social media, which fostered public distrust in any forthcoming vaccine.[3] Healthcare professionals, as trusted sources of knowledge, were called upon to optimize their social media platforms to reach more of the public with evidence-based information.[3] Since, popular hashtags attached to vaccination posts, like #educatedandvaccinated and #thisisourshot, suggest that healthcare professionals have indeed answered this call.[2]

Yet, a greater reliance on virtual communication in this pandemic has highlighted the complexity and uncertainty of social media as a tool for healthcare professionals.[4] The potential outcomes of improved vaccine uptake and reduced hesitancy originally sought by sharing one's SARS-CoV-2 vaccination status on social media may also come with inadvertent results. Additionally, there is a paucity of scholarly literature to support this emerging social media phenomenon. As such, this commentary considers what unintended consequences could arise from this promotional strategy and suggests alternative interventions to mitigate these effects.

A prominent concern around sharing vaccination status on social media is the perpetuation of panic and anxiety among those waiting to be vaccinated. Recognizing the role of social media in bolstering panic-buying and limiting personal protective equipment availability in the initial days of the COVID-19 pandemic, an inference may be made that a similar experience with the SARS-CoV-2 vaccine could arise.[5] Public stress while waiting to receive this ground-breaking vaccine may be exacerbated by social media users sharing their vaccination experiences and overrepresenting the actual number of people vaccinated.[4] As well, large volumes of vaccination-related posts may heighten fear of scarcity or misallocation, and invoke irrational behaviour to obtain the vaccine.[5] A New York Times article from December of 2020 reported city hospitals with limited supplies of the SARS-CoV-2 vaccine in initial rollout were experiencing increasing staff conflict and 'line jumping' to receive the shot, which relayed social media had played a role in mounting tensions.[6] Joseph Goldstein wrote, "...doctors and nurses have recalled scrolling through social media and pausing to make a snap judgment each time they saw a selfie one of their colleagues had posted of getting vaccinated: did that person deserve to be vaccinated before they were?"[6] The ability of social media users to consider their influence before posting vaccine-related content could be crucial in delineating these outcomes.

Recognizing the power differentials between healthcare professionals and the public, frequent posts of vaccinations may harm the mental health of those who cannot be vaccinated.[7] This concern especially arises from research indicating physicians with professional social media accounts, despite intentions to improve their audience's health behaviours, can exert paternalism and overlook patient autonomy in their content.[7,8] As such, patients with poor health or undesirable health behaviours may feel stigmatized, disempowered, or pressured to change from healthcare professionals online.[7-9] In the case of the SARS-CoV-2 vaccine, recurrent posts of vaccination status from healthcare professionals may likewise try to sway the public to get vaccinated, but then alienate those who cannot be. For individuals who are not eligible for vaccination, either due to age, a health condition, or residence, seeing many social media vaccination posts could result in increased feelings of judgement and mental isolation for not being able to post their own vaccination status.[10] Stigma for those ineligible to obtain the SARS-CoV-2 vaccine could also reduce care sought for COVID-19 and compound stigma among those already marginalized in society.[11] Professional guidelines surrounding social media use could be helpful in mitigating these circumstances. Ontario's College of Physicians and Surgeons offers a tangible example of such guidelines, requesting that members only share generic information on social media over personal experiences and opinions.[12]

On a similar thread, a lack of cohesion amongst healthcare professionals sharing their vaccination statuses online could reduce,

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rather than build, public trust in the vaccine. Research examining COVID-19 knowledge among healthcare professionals reveals varying levels of understanding of and acceptance for the vaccine.[13,14] Combining these differences in healthcare professionals' opinions with the fact that social media posts can be sparse in detail and lack credible sourcing creates greater potential for dissonance in the SARS-CoV-2 vaccine online narrative.[15] A healthcare professional may not even realize they are providing misinformation or have an opinion that is opposing vaccination because false news has been so prevalent on social media throughout this pandemic.[11] Instead, a more successful method of using social media during a vaccine campaign is to have specialized experts produce unified, balanced social media posts and address comments cohesively.[3] Oversight from platform creators will also help to effectively promote and share the posts of these experts.[2,16]

The SARS-CoV-2 vaccine is undoubtedly one of the most significant innovations in modern medicine, and it is critical now that vaccine hesitancy is reduced globally. For vaccine uptake, there likely will be positive outcomes seen from healthcare professionals sharing their vaccination status through social media platforms, but the concurrent undesirable outcomes are not fully understood. Research on this specific topic, important not only during the COVID-19 pandemic but also during periods of healthcare innovation and rapid development, should be conducted in order to inform healthcare providers' roles on social media. Until analysis occurs, healthcare professionals should utilize their social media platforms with caution and explore other means of promoting the SARS-CoV-2 vaccine. Validated methods of vaccine promotion may be of greater utility and include improving accountability for social media companies that allow the sharing of antivaccination ideologies, creating standardized messaging for international public figures and organizations to share, and offering the public vaccine counselling with an infectious disease specialist.[3,16,17]

Conflict of interest

The authors have declared no conflict of interest.

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Vaccines for cocaine addiction: Where we're going and why doctors should pay attention

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Abstract

Pharmaceutical options for stimulant and cocaine use disorders are profoundly lacking. To date, trials of numerous drug classes, including antidepressants, antipsychotics, psychostimulants, anticonvulsants and dopamine agonists, have been unsuccessful. However, research in this area is rapidly evolving, and yields interesting and varied results. The current article gives an overview of one of the latest pharmacotherapy modalities for cocaine use disorder: the cocaine vaccine.

For decades, pharmacotherapy has been recognized as an efficacious treatment for substance use disorders. Health Canada has approved medications for alcohol use disorder, including naltrexone, acamprosate and disulfiram,[1] as well as for opioid use disorder, including methadone, buprenorphine, naltrexone, and injectable hydromorphone.[2,3] However, pharmaceutical options for other substance use disorders are profoundly lacking. This is particularly concerning for cocaine and other stimulants, which account for a disproportionate burden of disease in Canada.[4]

Cocaine and other stimulants have been repeatedly implicated in the North American drug overdose crisis.[5] In 2020, stimulants were identified in 60% of Canadian opioid overdose deaths.[6] From 2016 to 2020, there were nearly ten thousand hospitalizations due to stimulant-related poisonings.[6] Some early evidence indicates that these numbers may be rising during the COVID-19 pandemic, as from January to June 2020, stimulant-related poisoning hospitalizations increased by 46%.[6] Thus, there is an urgent need for increased treatment options for cocaine use disorder (CUD). Though no pharmacotherapies are currently approved for CUD in North America, the potential public health and individual impacts of approved medications would be substantial. To date, trials of numerous drug classes including antidepressants, antipsychotics, psychostimulants, anticonvulsants and dopamine agonists, have been unsuccessful in treating CUD.[7] However, research in this area is rapidly evolving, and yields interesting and varied results.[8] One of the latest pharmacotherapies for CUD is the cocaine vaccine, which is unique in its mode of action and exists for no other substance use disorder type.

As early as the 1990s, rodent studies began to test the potential utility of cocaine vaccines.[9] These vaccines induce an antibody response to cocaine, with the intention of reducing cocaine in the bloodstream before it reaches brain tissue. The first vaccine trialed in humans, termed TA-CD, was made from succinyl norcocaine, a metabolite of cocaine, linked to a cholera toxin.[10] However, the vaccine was found to be effective in only a subset of patients who were sufficiently motivated to reduce their cocaine use.[11] Those without sufficient motivation were able to override the vaccine's blockade effects, potentially highlighting the importance of counseling and ancillary supports in maintaining motivation of pharmacologic treatment. Moreover, sufficient antibody levels lasted for only two months. Some limited evidence indicates that the TA-CD cocaine vaccine may be more effective in individuals with a particular κ-opioid receptor (OPRK1) gene, which has an allele that is protective against cocaine and opioid use disorders.[12] Though more research is needed, these findings suggest that in the future, effective use of TA-CD for the treatment of CUD could involve genetic testing. The TA-CD vaccine may be a much more promising treatment for those with particular OPRK1 genotypes than others.

In 2016, a new CUD vaccine, termed the dAd5GNE vaccine, began human clinical trials.[14] This vaccine is composed of a cocaine hapten, named GNE, linked to a surface protein of disrupted adenovirus.[14] Though the trial's estimated primary completion date is May 2021 (two months subsequent to the authorship of this article),[15] a recent study of mice and African Green monkeys demonstrated that the dAd5GNE vaccine effectively prevented cocaine from reaching the central nervous system in animals with daily moderate cocaine use.[14] Vaccinated mice with binge cocaine use had decreased cocaine-induced hyperactivity and seizures. Questions around the longevity and efficacy of these effects in humans remain unanswered, but this is an exciting and ongoing area of research.

Undoubtedly, a vaccination approach, and pharmacological approach more generally, would be just one of many tools for the treatment of cocaine use disorder. Robust addictions care involves evidence-based behavioral interventions (e.g., cognitive behavioral therapy) and accounts for the wide range of social, political, familial and other environmental and individual factors that contribute to recovery.[8] However, as research progresses, pharmacotherapy will likely begin to play a role in this treatment. As stimulant-related overdose deaths and hospitalizations continue to increase across North America, clinicians should welcome the entry of novel therapies to their practice.

Conflict of interest

The authors have declared no conflict of interest.

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Microbiome modulation through fecal microbiota transplant: A strategy to overcome melanoma immunotherapy resistance

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The successes and drawbacks of immunotherapy treatment for melanoma

Immunotherapy using immune checkpoint inhibitors (ICIs) has demonstrated clinical efficacy against various types of malignancies in the past decade and has revolutionized the field of cancer therapeutics. ICIs are monoclonal antibodies (mAbs) that inhibit immune checkpoint proteins manipulated by cancer cells to facilitate evasion from the immune system. Standard agents include mAbs directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and programmed death-ligand 1 (PD-L1).[1,2] ICI therapy has been particularly successful in treating melanoma, a type of skin cancer affecting melanocytes, which has resulted in markedly improved outcomes for patients with advanced or metastatic disease.[3] Despite this success, a significant subset of melanoma patients remain resistant to immunotherapy, as only 10–40% of patients with advanced melanoma respond to ICI monotherapy and 40–60% to combination therapy.[4–6] Multiple factors can contribute to ICI resistance, such as the mutational landscape and microenvironment of the tumour. Recent studies have also identified the intestinal microbiome as an important influence of ICI resistance, and there is growing interest in the therapeutic potential of microbiome modulation via fecal microbiota transplant (FMT) in cancer treatment.[7] This article aims to highlight the relationship between the intestinal microbiome and ICI therapy, and the current research on the use of FMT in improving ICI response rates in melanoma.

Influence of the intestinal microbiome on immunotherapy response

The intestinal microbiome consists of all microorganisms that inhabit the human gastrointestinal tract, and it plays a significant role in the regulation of immune responses. While the exact mechanism is still unclear, it is hypothesized that the intestinal microbiome can contribute to anti-tumour immunity by promoting the activation, proliferation, and migration of antigen-presenting cells and T cells to the malignant site.[8,9] Several studies have shown that recent or concurrent use of various broad-spectrum antibiotics is linked to poor response to ICI therapy and worse outcomes.[10–12] Antibiotics are known to induce gut dysbiosis by altering the composition and diversity of the microbiome, suggesting that the normal intestinal flora is involved in modulating immune function and thus modifying the therapeutic effect of ICIs. Other studies have identified certain intestinal bacterial taxa associated with improved efficacy of ICI therapy in melanoma, such as Bifidobacterium, Fecalibacterium, Bacteroides, and Ruminococcaceae species.[13–19] Some of these bacterial taxa have also been previously associated with increased anti-tumour immunity, suggesting a favourable bacterial profile in the gut may improve ICI response rates by stimulating an inflammatory response.[8]

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The use of fecal microbiota transplant to improve immunotherapy resistance

Although there are several ways to alter the composition of the intestinal microbiome, the most direct method is by FMT.[20] FMT involves the transfer of fecal material containing intestinal microbiota from a healthy donor to the gastrointestinal tract of a recipient to directly modify their microbial composition.[21] Results from two phase 1 clinical trials have demonstrated the benefit of FMT in improving treatment response in patients with ICI-refractory melanoma. The study by Baruch et al. involved performing FMT on recipients with anti-PD-1 refractory melanoma using donors who had been successfully treated with anti-PD-1 therapy for melanoma.[22] Three of the ten recipients responded to subsequent anti-PD-1 therapy, as demonstrated by tumour size regression. A similar study conducted by Davar et al. found that three out of 15 patients with anti-PD-1-refractory melanoma responded to anti-PD-1 therapy after undergoing FMT.[23] Further, both studies found that recipients who were responders had favourable changes in their immune profile, as shown by upregulation of pro-inflammatory gene expression and increased infiltration of immune cells within tumours. Further, there were minimal treatment-related adverse events reported. As of February 2021, these are the only published reports from human clinical trials demonstrating the efficacy of FMT in combination with anti-PD-1 therapy to treat melanoma. These results are promising and highlight FMT as a potentially safe and beneficial adjunctive approach to consider for patients with ICI-refractory melanoma.

The future of microbiota modulation in immunotherapy treatment

The most well-known clinical application of FMT is in the treatment of Clostridioides difficile infection (CDI), where it has shown success with an average cure rate of 80–90% and is currently indicated for CDI that is unresponsive to conventional therapies.[24,25] Previous randomized trials have also reported that FMT for the treatment of CDI is generally safe with relatively few minor side effects including diarrhea, constipation, bloating, and abdominal cramps.[24] Serious adverse events have rarely been documented.[26] More research will be needed as data on the long-term health effects of FMT are limited. For example, larger clinical trials with extended follow-up will likely be required to evaluate the efficacy and safety of FMT in a greater population.

Despite limited success in recent clinical trials, the research on the use of FMT as an adjunctive treatment for melanoma is still in its early stages. There are several significant limitations to FMT, as the mechanisms underlying its effect on microbiota composition and ICI response are not well understood. Furthermore, FMT likely has limited effectiveness in treating ICI resistance caused by factors external to the microbiome, such as tumour-intrinsic or genetic factors. Therefore, FMT may be beneficial only for a subset of patients, and further research is needed to better characterize and identify this patient group. Suboptimal FMT can also occur as the fecal material in FMT may not

exactly represent the donor intestinal microbiome, and the recipient microbiome may interfere with the colonization of transplanted bacteria, which may contribute to low FMT success rates.[27] Alternative methods that may be used in the future include developing probiotic agents to increase the abundance of favourable bacteria and selectively deplete unfavourable bacteria with antibiotics or bacteriophages.[9] Despite its drawbacks, targeting the intestinal microbiome remains an exciting but experimental strategy in the treatment of ICI-refractory melanoma, and these recent studies have improved our current understanding of how the microbiota can play a role in ICI resistance.

Conflict of interest

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Effects of the COVID-19 pandemic control measures on the human microbiome

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Introduction

It has now been over one year since restrictions to limit the spread of COVID-19 were implemented around the world. Each region has introduced their own policies based on local need and resource availability, broadly under the directives of physical separation, increased hygiene, and other initiatives to influence public behavior. While these measures have played a definitive role in controlling infection rates and COVID-19 mortality there is trepidation on how such large changes in human behavior will affect our long-term health. In particular, the human microbiome has become a focal point for health research and care practices given its inextricable, yet not fully understood, relationship with us as hosts. The microbiome is comprised of trillions of symbiotic microbial cells harbored within each person, primarily in the gut.[1] Decreased diversity and maladaptation, known as dysbiosis, has been associated with noncommunicable conditions including obesity, malignancy, asthma, cardiovascular, neural, and autoimmune diseases.[2] This article will explore the current perspectives on how pandemic-driven changes might influence our microbiomes.

Microbiome and lifestyle changes

The wellbeing of the human microbiota relies on a dynamic balance between acquisition and loss of species, which is maintained through lifestyle factors that generate exposure to new healthy microbiota candidates.[3] For example, increased diversity in microbiome composition has been found in people living in remote rural settings, living with non-sedentary lifestyles, and with varied social connections.[4] However, pandemic control measures have largely geared people away from these lifestyle characteristics. The pandemic has introduced an unprecedented decrease of mobility and social interaction brought upon by stay-at-home orders, social distancing, and closure of public spaces. Studies also suggest that pandemic factors have led to a decrease in physical activity and increased sedentary behavior in both North American adults and children.[5,6] Where the trend towards urbanized living and subsequent increases in sedentary lifestyles has already been linked to rise in noncommunicable conditions that are partially attributable to poor microbiome health, there is concern that isolation-oriented pandemic measures can lead to the increased burden of these conditions.[7]

Increased use of disinfectants

Cleaning has been an essential part of public pandemic control for high-density public locations and was zealously adopted by many individuals at the start of the pandemic.[8] However, disinfectant products are unable to differentiate between harmful and useful bacteria, and frequent use of commercial detergents can disrupt environmental and human microbiomes. The Canadian Healthy Infant Longitudinal Developmental cohort study previously showed correlation between increased home environment disinfection and increased biofactors for childhood obesity.[9] Disinfection was also found to contribute to increased antibiotic resistance, as use of minimal inhibitory concentrations of antimicrobial agents can induce transfer of resistance genes.[10] The pandemic-driven spike in disinfectant use may exacerbate this disruption to microbiomes and impact our long-term health.

Impact on vulnerable populations

The harm experienced during this pandemic is disproportionately worse for vulnerable populations. In addition to the racial and economic inequality in COVID-19 infection rates and mortality,[11] the experiences with food, housing, and job insecurity as well as the myriad of other challenges faced by vulnerable populations will have long-lasting health effects that include the human microbiome. Prior to the pandemic, vulnerability factors such as inadequate housing in urban settings, water insecurity, poor waste treatment, and overcrowding were found to correlate with compositionally different and less diverse microbiomes.[12] These factors were amplified by the pandemic, in particular for populations previously affected by these risk factors.[13,14] As well, due to exacerbated economic hardship and disrupted food supply chains,[15] people are consuming increasingly irregular diets of processed, low-fiber foods which may lead to microbiome dysbiosis.[3] The stress of the pandemic and its precipitating obstacles can build towards a reciprocal cycle of stress-related disorders and poorer health, of which microbiome damage may play an important role.[16]

Future directions

There is a need to better understand how pandemic control measures can impact our susceptibility to health conditions as they relate to our microbiome. As there are currently no definitive indications of how we will be affected in the "post-COVID-19 era", health authorities should consider the effects of microbiome damage within the context of preventing infectious spread. Public education can help individuals understand how they can maintain healthy practices within restriction guidelines. Evidence-based advice on how to sustain non-sedentary routines and safely engage in social interactions can help the public adapt to pandemic lifestyle changes. Standards on disinfection can be disseminated to help organizations and individuals understand the level needed to protect public and private spaces without damaging peoples' health. Through the context of the microbiome, it is reemphasized that vulnerable populations suffer disproportionally in crisis as seen in the COVID-19 pandemic and require equitable support to meet their needs. Additionally, remedial approaches for dysbiosis, such as encouraging the consumption of foods and probiotics that promote microbiota diversity,[17,18] should be studied and considered as we approach pandemic recovery. Overall, we need to balance the battle against the COVID-19 pandemic with the need to maintain our long-term health, including the health of our microbiomes.

Conflict of interest

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Applying machine learning to abstract screening: Reducing the workload associated with systematic reviews

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The words "systematic review" can evoke different emotions. As clinicians-in-training, we recognize their immense value in synthesizing the current literature, yet the thought of conducting a systematic review can recall the image of sitting in front of a computer screen, scrolling and clicking for hours on end. Is this work important? Absolutely. A high-quality systematic review effectively summarizes evidence and guides clinical practice. Is it always enjoyable work? We will let you answer that one. Given the repetitive and time-consuming nature of systematic reviews, a natural question emerges: can this process be automated and still yield valid results?

All systematic reviews should begin with formulating a clear, structured, and relevant research question.[1] A comprehensive, reproducible protocol is then created, which outlines the criteria for the literature search, study selection, and data extraction and synthesis.[1] After extensively searching multiple databases for papers that meet the inclusion and exclusion criteria, each selected paper is subjected to a rigorous quality assessment according to a critical appraisal guide and categorized into a quality hierarchy according to how well it fits with the pre-established criteria. Afterwards, the relevant data are extracted and synthesized to examine the differences, and if appropriate, combined using statistical analysis to present as a meta-analysis.[1]

Currently, major advancements in the automation of systematic reviews are centered around optimizing the search and screening process. Machine learning (ML) systems can easily be used to assess article relevance and classify randomized controlled trials (RCTs) by searching the document for weighted identifiers.[2] RCT classification systems, such as RobotSearch, have been shown to be more accurate than conventional search filters. Compared to the Cochrane Highly Sensitive Search Strategy, RobotSearch has been shown to decrease the number of retrieved irrelevant articles by nearly half without losing any additional RCTs.[3] In addition, ML algorithms have already been incorporated into database search engines, including PubMed.[4] Specifically, the Best Match feature of PubMed presents the most relevant abstracts at the top of the results page. This feature uses inputted search terms to calculate a weight for each article depending on factors including the number of times the term appears and the date of publication.[4] The issue with these algorithms is that the user can miss potentially relevant articles if they do not explore the entire output of the search.[4] The limitation of these sources, and consequently the prioritization of the higher weighted articles, can lead to anchoring and recency bias.

ML systems can also be trained to suggest topically relevant papers, which are then validated by a human reviewer in a semi-automated cyclical screening process, as described below.[2] Data extraction ML tools, although in early stages of development, will also most likely involve a similar semi-automated process. For example, RobotReviewer can appraise RCTs and extract text describing key trial characteristics related to the research question and reliability measures.[5] Although researchers are working on developing ML that is capable of extracting and synthesizing data, these remain in their formative stages compared to the more mature and robust text classification systems that perform searching and screening tasks.

In this letter, we will focus on how ML is being used to optimize the process of screening and appraising abstracts, which has received the largest focus to date.[6] Manual abstract screening does have its challenges. Unless the researcher is well-versed in the search engine tools and indexing standards of various databases, they are likely to miss papers that are absent in their database of choice.[7] Even with advanced search filter options, online searches often yield a vast number of irrelevant results that require manual sifting. Given the repetitive nature of this task, ML tools have been proposed as a potential solution to expedite this process, with publications on this topic dating back to 2010.[8-11]

Current ML abstract screening tools are semi-autonomous, requiring a human researcher to import the abstracts into the software's platform and label a set of abstracts as relevant or irrelevant as part of the ML training process.[6] After an initial training step, these tools can screen study titles and abstracts according to the researcher's ongoing study selections.[2] These programs can be used to prioritize relevant papers for the researcher to review or they can function as a second reviewer to improve screening accuracy.[2] Importantly, the training process continues as more studies are accepted or rejected by the researcher.

Two well-known ML abstract screening tools that have been validated in former studies are Abstrackr and RobotAnalyst.[12-13] Gates et al. compared the performance of these two programs and concluded that they were able to save 85–90% and 35–40% of the total workload when used as the sole-reviewer or as the second-reviewer, respectively.[2] For usability, Abstrackr had a higher subjective score than RobotAnalyst based on eight study participants ranking each program's interface, ease-of-use, and features.[2] Based on factors including review topic, number of abstracts, and screening complexity, the sensitivity, specificity, and precision of Abstrackr can range from 79–96%, 19–90%, and 15–65%, respectively.[14] These tools are currently being used in practice and have been included in studies published in Annals of Internal Medicine,[15] Obesity,[16] and the American Journal of Obstetrics and Gynecology.[17]

Despite their efficacy, the growth of ML tools for abstract screening is met with some key barriers. Widespread adoption of these tools may be challenged by a lack of trust in its black box decision-making algorithm or difficulties with setting up the program and determining the extent of training required to elicit accurate responses.[6,18] If researchers perceive an increased risk of rejection by journal editors, adoption of these ML-based programs is less likely even if the tools are validated to yield results comparable to conventional methods.[2,18] Finally, the program also needs to be able to recognize different study designs. Currently, it is harder to automate the recognition of different types of non-RCT studies.[2]

To quote Marshall and Wallace, "full automation remains a distant goal at present."[6] Despite the strides made in the field of systematic review automation, the automation of steps proceeding abstract screening

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requires further investigation. However, these tools are continuing to be developed, improved, and validated. Perhaps these ML tools, like all new technological advancements, require early adopters pioneering their use and identifying gaps for improvement. Perhaps, this could be where medical students tasked with conducting a systematic review step in.

Conflict of interest

The author has declared no conflict of interest.

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Presumed consent in organ donation: The next step for Canada?

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On January 18th, 2021, Nova Scotia became the first jurisdiction in North America to shift from an expressed consent system (ECS) for organ donation to a presumed consent system (PCS).[1] The Human Organ and Tissue Donation Act of Nova Scotia considers every adult an organ donor by default upon death unless they choose to opt-out. Currently, the deceased organ donation rate in Canada, which has a high degree of variability in family consent rates, is less than half the rate of top-performing countries such as Spain.[2] The hope is that the initiative will address the disparity between organ supply and transplantation demands and ease the burden of decision-making on families at the time of death. PCS then may become the catalyst for other Canadian provinces and territories to adopt a similar policy in the future. However, its implementation does raise ethical and practical concerns.

The movement for PCS in Nova Scotia began in 2017 when the province had a record low number of just 16 organ transplants in the entire year. At this juncture, a collaboration between Dr. Stephen Beed, medical director of Nova Scotia's Organ Donation Program, and the Premier of Nova Scotia, Stephen McNeil, took place to adopt the PCS policy.[1] Individuals who do not wish to participate in PCS can register to opt-out. Families can also intervene to halt the organ donation process. Currently, the plan will apply to adults over the age of 18 and exclude children as well as those who lack the competency to understand that they are automatically giving consent.[3] Temporary residents of Nova Scotia, such as out-of-province or international students and workers are also exempt.[4]

PCS for organ donation is not a novel concept. Growing frustrations over lengthy transplant waiting lists have prompted countries such as Spain, Italy, France, and several others to enact the legislation in the past.[5] In general, these countries have seen success in addressing organ shortages through PCS. One highly cited study looked at 22 countries with PCS over ten years and found that after controlling for confounders, organ donation rates were 25-30% higher in PCS countries compared to ECS.[6] Another study comparing all 4 UK nations observed that Wales, having enacted PCS in 2015, saw a higher organ donation rate in 2017 compared to the other 3 UK nations based on ECS.[7]

Critics argue, however, that PCS alone may be inadequate to address organ shortages.[8] Indeed, positive organ donation rates may depend on a combination of factors, including the efficiency of a country's transplant infrastructure, transplant policies, and attitudes toward organ donation.[9] For instance, authors of the Wales study point out that change in legislation may not be the sole factor for positive results in a country which has been steadily making an effort to improve their organ donation infrastructure as well as communication strategies since 2008.[7] Furthermore, family members who intervene on their deceased relative's behalf may view PCS unfavorably and refuse organ donation. When asked, family members admit that they perceive the donor's underlying preference to donate as being stronger when there is expressed rather than presumed consent, regardless of which country they originated from.[10] A study examining family refusal of organ donation in the United Kingdom between 2016 and 2017 showed that the consent rate is higher (91.2%) if the deceased had willingly registered as an organ donor compared to those who died without being registered donors (46.7%).[11,12] However, the literature also offers counter evidence using data from 28 countries showing that there are lower family refusal rates in countries that have adopted PCS (29.7%) compared to countries with ECS (38.9%).[13]

Moreover, the perceived loss of patient autonomy in PCS is a concerning ethical matter.[5] A proportion of patients may be uncomfortable with allowing their deceased body to be invaded without informed consent. Meanwhile, others feel strongly that legislating PCS would violate freedoms guaranteed by their constitution, such as the 5th amendment in the United States prohibiting the usage of private property for public use.[5] In response, proponents of PCS argue that it increases patient autonomy as it shifts decision-making from the family to the donor, thereby alleviating unnecessary uncertainty and anxiety at the time of death.[14] Supporters also offer a utilitarian argument which suggests that a PCS policy is morally superior as it provides the most benefit for the most number of people.[15]

PCS may be worth considering for British Columbia (B.C.). Last year, despite the COVID-19 pandemic, B.C. had a record number of heart and lung transplants in 2020.[16] In total, 451 people in B.C. received a transplant last year, compared to 480 in 2019, and 502 in 2018; 700 patients are currently on the waiting list.[17] There are several factors that contributed to the increased number of heart and lung transplants in B.C. last year. Firstly, there has been a shift in how ICUs are handling organ donations. It is now considered an end-of-life option and offered to anyone who could be a potential organ donor.[16] Secondly, a proportion of organ donors have been the victims of the ongoing opioid overdose crisis, with a record 1,716 illicit drug deaths in 2020.[18] Of course, waiting on additional organs from overdose victims is not ideal, and efforts are underway to manage the opioid overdose crisis.

Canada may soon follow as Nova Scotia takes the lead in the organ donation frontier with PCS. Studies investigating the impact of PCS on other nations suggest that it is a superior policy to ECS when it comes to organ donation.[6,7,11] It is therefore prudent to consider PCS as a wise means of increasing organ donation throughout Canada. However, it is important to mention that PCS may not be a singular solution to the organ shortage problem. Organ donation is influenced by multiple factors such as public health campaigns, improved infrastructure, organizational changes, and family communication strategies. Ultimately, reducing wait times for transplants in Canada will require a multifactorial approach and PCS remains a promising addition to change in this endeavor.

Conflict of interest

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The mouse is mightier than the pen: How electronic medical records have shaped modern medicine

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The medical record has existed in some form for nearly 4000 years, with the earliest known documents dating back to an Egyptian surgical case report written on papyrus circa 1600 BCE.[1] It was not until the early twentieth century, however, when hospitals started adopting medical records as legal documents.[2] Since then, the medical record has continued to undergo significant changes, the most notable of which occurred with the introduction of electronic medical records (EMRs) in the mid-1990s.[3] Conceived as the digital solution to the myriad of challenges inherent to paper medical records, EMRs, also known as electronic health records, have seen physicians around the world trading in their writing utensils for computer mice at an unprecedented rate. In a 2018 survey of Canadian clinicians, 84% of primary care physicians and 89% of specialists reported using EMRs in their medical practice to varying degrees.[4] Although significantly increased from the estimated 73% uptake among Canadian primary care physicians in 2015, Canadians still lag behind their medical counterparts in ten other developed countries, whose EMR use among primary care physicians ranges from 88% (France) to 100% (New Zealand, Norway, and the U.K.).[5] Moreover, interprovincial EMR usage among primary care physicians varies greatly, with the territories leading the way at 96% and Prince Edward Island trailing behind at only 26%.[5] Among those who have yet to digitalize their records, reported barriers include training limitations, insufficient computer literacy, security concerns, and a lack of interoperability with other EMRs.[6] Despite the reservations of some, most Canadian physicians indicate that EMRs have allowed them to provide more efficient care.[5] Other commonly cited benefits include fewer unnecessary or duplicate tests and improved patient care and safety, particularly among those with chronic conditions or complex medical histories.[6]

Despite its prominence within the Canadian healthcare system for over two decades, EMR software remains in its adolescence. Among other concerns, physicians have listed poor software usability, burdensome documentation, and information overload (also known as "alert fatigue") as driving factors behind their dissatisfaction.[7,8] Closely related is the notion of "desktop medicine," which posits that EMRs have contributed to the ever-growing amount of time that physicians spend in front of a computer. In fact, U.S. studies have shown that physicians across specialties spend more than half of their daily working time in front of a screen.[9,10] Consequent to this shift into the digital world is an increase in physician burnout, which has consistently been associated with EMR use and inversely related to career satisfaction among Canadian physicians.[11,12] Surveyed physicians also generally agree that the human element of the physician-patient relationship has suffered since the uptake of EMR systems.[13–15] Whether it be through reduced eye contact during clinic appointments or the disproportionate time spent treating the electronic patient charts rather than the patients themselves, the therapeutic culture of the physician-patient relationship has been unarguably altered by the EMR.[16] Reassuringly, this shifting dynamic has generally not contributed to patient dissatisfaction, with most patients recognizing the benefits of EMRs and emphasizing the importance of physician attention over eye contact.[17–19]

Another of the more substantial limitations to EMRs has been a lack of interoperability, or an inability to share patient health data outside of one's immediate practice setting. As a consequence, both community and hospital-based physicians are often left struggling to piece together a patient's history, leading to costly retesting, reduced efficiency, and medical errors.[20] This has particularly held true in the Canadian setting, where only 25% of primary care physicians have the ability to electronically exchange patient data with other providers compared to the 63% average across 11 developed countries.[5] While provincial eHealth viewers have offered a partial solution by providing access to integrated patient data across various regional health authorities (such as CareConnect in British Columbia or ClinicalConnect in Ontario), they are largely limited to hospital records and fail to incorporate primary care and other community-based healthcare information into their databases.[21,22] As a result, some have suggested implementing a single national EMR system to facilitate the sharing and transfer of patient information across jurisdictions and clinical settings.[23] Others have raised concerns with the feasibility of this approach and have instead suggested improving the interconnectivity of current EMR systems with a comprehensive and centralized national health database.[20,24] Regardless of the proposed solution, both parties agree that changes are critically needed. This opinion is shared by family physicians across the country, 65% of whom identify improved integration of primary care with other healthcare services as their top priority in improving overall health care quality.[5]

Although the limitations of modern EMRs have certainly dampened physicians' enthusiasm towards them, the benefits of efficient medication management, legible clinician notes, and organized and complete patient charts cannot be overstated, especially amid an aging and increasingly medically complex population.[25,26] Accordingly, the vast majority of Canadian physicians agree that EMRs have improved their overall practice and would not return to a paper-based practice if given the opportunity, particularly among those whose EMR use extends beyond one or two core functionalities.[4,27] Advanced features such as screening and immunization reminders, drug dose and interaction warnings, and other automated disease management and prevention tools have further added to the benefits of EMRs, and have been shown to improve the delivery of high-quality health care by clinicians.[28,29]

Regardless of one's opinion on the matter, none can dismiss the sheer impact of EMRs on modern medicine. Indeed, the past two decades have seen EMRs evolve from the fringes of medicine to the powerhouse that sits at its core. This evolution is far from finished, however. As time marches on, the EMR must continue adapting to the ever-changing landscape of modern medicine. While the financial costs of these endeavors are likely to be substantial, the unprecedented COVID-19 pandemic has starkly illustrated the importance of EMRs and other

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digital solutions in solving emerging global healthcare challenges in which timely access to clinical and research data can mean the difference between life and death.[30,31] Despite their many shortcomings, EMRs have fundamentally advanced the way physicians navigate healthcare – transcending the imaginations of our papyrus-wielding predecessors and proving once and for all that the mouse is mightier than the pen.

Conflict of interest

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Commentaries are intended to provide a platform for intellectual dialogue on topics relevant to the study and practice of medicine. Submissions should correspond to one of the following categories:

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- Clinical perspectives on an interesting research study or area of focus.

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