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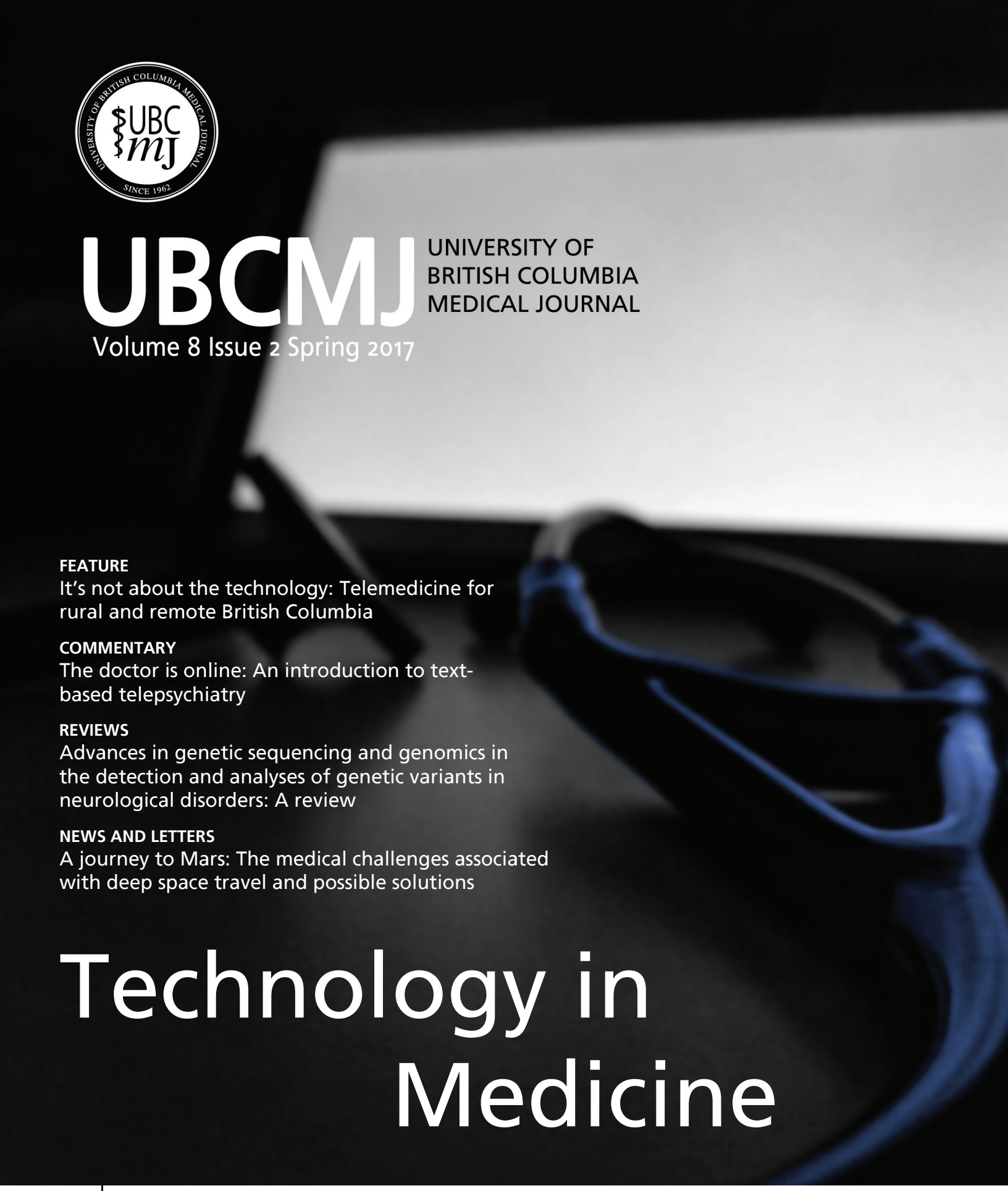

Technology in Medicine

THE UNIVERSITY OF BRITISH COLUMBIA

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On the cover

The advent of new technology is often associated with providing solutions to our problems. However, with new advances brings new questions, and we are left navigating an increasingly complicated world – searching for relevance amongst distractors. In medicine, as we utilize these new tools, procedures and knowledge, it is important that we maintain our focus on what is important. We must not allow our technological optimism to overshadow the foundations of medicine and patient-centered care.

In this issue we explore some of the exciting technological developments that are occurring in medicine, along with the implications that they bring to practicing medicine in the modern world.

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Moving forward: Technology in medicine in 2017

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One of medicine's greatest challenges in the 21st century is to maintain pace with the incredible steps of advancing technology. In only the past few years, scientists, with the help of rapidly changing technology, have used brain–spinal interfaces to restore locomotion, engineered chips that mimic brain function, manipulated memories, and altered human embryos using a powerful technique known as CRISPR.[1-4] These incredible advances have certainly increased our understanding of human biology, but their translation to clinical medicine can often take decades. The aim of this issue of the University of British Columbia Medical Journal (UBCMJ) is to explore the challenges and inform on the interplay between technology and medicine as these fields align to keep our society healthy. We also hope to identify areas of healthcare that are in critical need of support from recent technological advances.

Although changing technology has the potential to revolutionize the standard of medical care, medicine may be lagging behind due to a variety of reasons. Technology is changing the way that we communicate and this has a multitude of bearings on the ways that medical care is delivered. With alternative modes of delivering medical care such as telemedicine or text–based medicine, issues with confidentiality and familiarity with the technology may affect the adoption of such services.[5] Information is also now widely available to the patient population and accessing their own medical information online may impact a patients' perceptions of disease and expectations for treatment.[6] Sometimes, technological solutions fail to be adopted simply because of logistical barriers. Indeed, this may be the case with standardized electronic medical records, which still remain to be adopted universally nationwide in a centralized fashion.[7] Some technological feats related to medicine may simply still be out of reach, such as the technology that would be required for sending humans on extended outer–space journeys. The articles contained in this issue touch on these topics by discussing the navigation of a world of online health information, how Canadian healthcare is faring in regards to advancing technology, and what the future may be looking like for fields such as space medicine and genomics.

Our feature articles further discuss the complexities of adopting technology in medicine from various angles. Dr. Copley comments on how technology is changing telemedicine and why a focus on the medicine, and not the changing technology, may be advantageous. Adam Ramzy discusses how gene therapies are rapidly moving from bench to bedside for the treatment of conditions such as hemophilia, rheumatoid arthritis, and other genetic disorders. Moreover, Dr. Vogl discusses the challenges of maintaining a strong anatomical education in the face of the dynamic medical school education playing field. We hope that this latest issue of the UBCMJ provides a discussion of the adoption of technology in medicine and how medical students and future physicians can be involved in contributing to the technological revolution in medicine.

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The state of gross anatomy

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"To dissect or not to dissect?"—that is the question. Although students in many medical schools are still exposed to at least some dissection as part of the process of learning Gross Anatomy, curriculum leaders are increasing the pressure on faculty to replace dissection with alternative methods such as prosections (professionally dissected isolated body parts) and various forms of digital media. In part, this pressure is the result of an increase in breadth of content related to medical training, changes in curricular design, and the high costs associated with running dissection laboratories.

At the University of British Columbia (UBC), our Gross Anatomy program has dramatically changed since the early 1980s when the discipline was a course of around 300 scheduled hours and ran three half days a week for the entire first year. When we transitioned to a blended Problem–Based curriculum in the late 1990s, all basic science courses were eliminated as stand–alone courses and Gross Anatomy was integrated into systems blocks that ran for two years. The total time for the Gross Anatomy program was decreased to around 120 scheduled hours (Figure 1). Although Gross Anatomy was still taught with lectures and dissection laboratories, the way in which the material was covered changed. Gone were the more traditional anatomy lectures where one emphasized the anatomy itself and structures were learned in-depth. In the newer curriculum, excessive detail was removed and sessions were focused on providing concepts of body design, presenting overviews of regions, and covering major clinically-relevant details. Dissection remained the primary method of learning; however, dissection sessions became more focused on meeting specific objectives. Prosections were included to illustrate material that was too difficult to dissect within the scheduled time constraints, or to illustrate certain concepts. Many of the dissections were "anchored" by specific activities that had significant educational value and long lasting impact. What student will ever forget opening the skull and seeing how tightly the dura mater adheres to bone, and seeing the brain and cranial nerves for the first time? Who could forget opening the vertebral canal, seeing the spinal cord and discovering that the cord does not extend the entire length of the vertebral column, or opening the thorax and seeing the heart and lungs for the first time, and discovering how "thin" the diaphragm is? Lectures and laboratories emphasized structure/function relationships and clinical significance rather than detailed anatomy. In the older traditional curriculum, the answer to the question, "What do I need to know?" was simply "Everything!" In this newer curriculum, the answer became, "It's in the learning objectives and in the laboratory checklist." Other changes that have impacted our gross anatomy teaching over the years have been an increase in class size from 120 in the early 1980s to almost 300 students at present, and our transition in the early 2000s to a distributed program where all students are present at UBC for the first three months and then cohorts move to three additional satellite campuses around the province for the remainder of their medical undergraduate training. We have anatomy laboratories and faculty at all sites and deliver interactive lectures and pre-lab talks to all sites via videoconference to large screens.

Our current curriculum, implemented in 2015, is Case-Based, where content is focused around the clinical case of the week. Total Gross Anatomy time over the first two years has been further reduced to approximately 70-80 hours (Figure 1). Lecture sessions on Diagnostic Imaging usually occur immediately after the lectures on Gross Anatomy, and imaging sessions are now included in the laboratories, many of which have been reduced from three to two hours. Certain Gross Anatomy content and dissection laboratories have been entirely deleted, and those

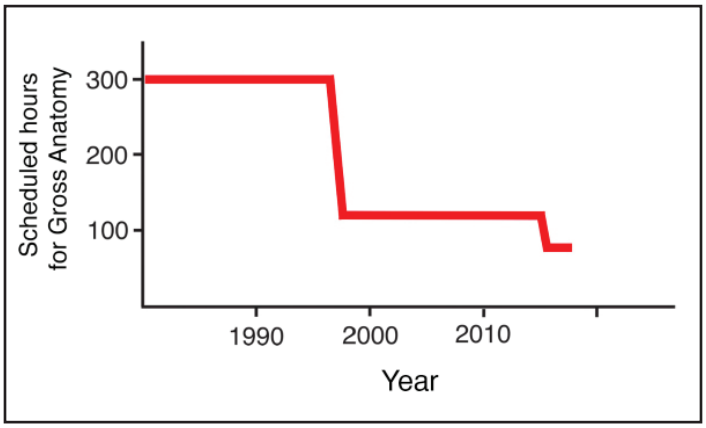

Figure 1 | Total scheduled hours of Gross Anatomy over the first two years of medical education from the 1980s to present.

that remain have been further refined to concentrate only on "significant" structures and on material "relevant to the case of the week". Although time is limiting, we have retained dissection as the cornerstone of learning. At each table, a group of six students participate in revealing the structures indicated by faculty, and in discussing the significance of their findings amongst themselves and with laboratory instructors and teaching assistants. Anatomy observed in the cadavers is correlated with "state of the art" imaging presented by radiologists at the new Sectra Visualization Table that enables three–dimensional reconstruction, rotation, and dissection of structures from CT and MRI data sets

The use of information technology has been embraced by faculty. Numerous digital resources, including online modules and videos, are being created to augment student learning. Interestingly, the use of high definition digital cameras in the lecture theatres has made "something old new again". Drawing and writing on the blackboard is captured in real time by the cameras and projected onto large screens so that even learners sitting at the back of the room, or at distributed sites, can see what is being done. In addition, most lectures are recorded, and PDFs or PowerPoint copies of lecture materials are made available on the student portal website prior to the presentation so that students can add notes to them on their mobile devices during the lecture. High definition cameras together with monitors in the gross anatomy laboratories enable instructors to orient students to the dissection during pre-lab talks and also to videoconference the talks to distributed sites.

My answer to the question "to dissect or not to dissect?" is a resounding "to dissect". In my opinion, none of the current digital forms of anatomy resources, including computer–based dissection programs, visualization tables, and virtual reality tools adequately replace the educational value of dissection laboratories. Also, for ethical, budgetary, and educational reasons, the use exclusively of prosections for 300 students spread across four sites is not a viable alternative to dissection. Digital resources and the selective use of prosections within the context of students using "intact" cadavers certainly augment dissection, but they do not replace it. There is so much more to developing a "working knowledge of anatomy" than simply memorizing a list of terms or identifying structures on pre–dissected isolated body parts, and much of this development occurs in the dissection laboratory. I believe we are at a critical time threshold required to do the minimal amount of dissection that results in a "professionally useful" working knowledge of anatomy. Any further reduction in scheduled time will compromise the respectful and ethically appropriate dissection of cadavers by students, and will likely result in the adoption of alternative and much less time–effective, cost–effective and learning–effective means of presenting the discipline. My response to those that argue we can no longer afford "to dissect" is that we cannot afford "not to dissect".

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It's not about the technology: Telemedicine for rural and remote British Columbia

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The Canada Health Act states that "The primary objective of Canadian health care policy is to protect, promote and restore the physical and mental well–being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers."[1] In many areas of rural and remote British Columbia, such barriers remain. Among the obvious are distance, weather, and ability to travel, all of which produce financial barriers. Moreover, the risk of travel should be appreciated. Telemedicine, defined as the delivery of medical care at a distance through telecommunication methods, can offer a solution; however, its successful implementation will not be driven by technological advances alone. We believe that effective and trusting relationships among patients, communities, primary care physicians, and specialists are the true essence of a clinically effective telemedicine system.

In the early 1900's, Einthoven provided one of the first examples of telemedicine by transmitting electrocardiograms over telephone lines.[2] While telephones are still widely used, other communication methods are now available, such as real–time video (i.e. video conferencing) and, more recently, store–and–forward, a system whereby clinical information is uploaded to a website and viewed later by a consultant physician. With the now widespread availability of high–speed internet and cellular networks in many rural areas, an unprecedented level of access to telemedicine is now possible. Conversely, those communities still without either internet or cellular service remain particularly deprived.

In recent years, Canada has seen record–high usage of telemedicine in most clinical specialties. According to the Canadian Telemedicine Report, there were 411,778 real–time clinical sessions (e.g. telephone or video link) in the year 2014, representing a major increase from the 282,529 reported in 2012.[3] This does not include the more than 41,863 store–and–forward sessions in 2014.[3] In British Columbia, 22,585 real–time and 27,123 store–and–forward clinical sessions were reported in 2014.[3] Compared to 2012, these numbers represent a slight decrease in real–time sessions but a substantial increase in store–and–forward sessions, suggesting a trend in favour of this newer technology. While the reasons behind this trend were not formally assessed, several factors might be at play. In a recent survey of dermatologists and primary care physicians, equipment costs, equipment management, and staff training—all factors that apply mainly to real–time telemedicine—were cited as barriers to its use for dermatology.[4] In contrast, store–and–forward requires minimal investment, as it makes use of basic equipment already in most physicians' offices (e.g. computer, internet access, and one or several peripheral devices). Furthermore, the asynchronous nature of the communication in store–and–forward systems adds the advantage that there is little to no scheduling needed on the part of the referring physician or the provider.

Whatever the method, a key to the effectiveness of telemedicine is to establish enduring relationships among health care providers. This has been shown to be an important factor in both primary care physician work satisfaction and optimal patient care.[5,6] As noted above, store–and–forward platforms are widely used and can be a highly effective method of communication for both consultants and primary care physicians. Telephones also continue to be a useful method of connecting physicians, as demonstrated by the expansion of the Rapid Access to Consultative Expertise (RACE) program.[7] With the nearly universal ownership of mobile phones, most of which are smart phones, clinical use of these devices, in our experience, is widespread, yet there is almost no data available regarding these practices. In one study of residents in Saudi Arabia, 64.4 % of respondents reported using their personal mobile phone as a primary form of medical communication; however, only 6.9 % had received formal training on the medical use of mobile phones.[8] Because there are significant advantages in terms of costs and convenience, personal mobile phones will likely play a key role in the delivery of telemedicine; however, since legitimate privacy concerns exist, standards and universal training should be put in place to protect patients and providers.

Regarding the establishment of telemedicine delivery standards in this province, those that best foster relationships between consultants and primary care providers should be encouraged. This may be accomplished through "telemedicine communities" representing rural areas, their associated primary health care providers, and designated specialists. One such community of practice being formed as a result of local planning and initiative is that by Carrier–Sekani Family Services.[9] This model is founded on a "bottom–up" approach, which thoughtfully matches telemedicine services to local conditions. In such a model, consultants visit the areas they serve, both to better appreciate local challenges and to forge relationships with local practitioners, patients, and the communities in general. Consultants and primary care providers connect for both elective and acute care services; the technology simply helps to stitch this tapestry of providers and patients together. The types of technology used can be decided by a given "telemedicine community" and inevitably are those that are most convenient and effective. In other words, the technology supports the model of care; it does not define it.

A consultation with a specialist is not only for clinical care but also an opportunity for education at the "point of care." Furthermore, when consultations occur in "real time," dialogues can promote both collegiality and education for specialists about the realities of rural and remote medicine. We also believe that there is potential for more immediate involvement of both allied health care professionals and the patients themselves.

Despite technical advances that allow unprecedented levels of interaction between patient and provider (e.g. use of peripherals such as digital stethoscopes and otoscopes), telemedicine likely will never—and should never—replace traditional in–person consultation when this is reasonably accessible. In rural and remote British Columbia,

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in–person consultations are frequently inaccessible by any reasonable standard. We argue that telemedicine should always be considered in the care of such patients.

Telecommunication technologies continue to improve and in fact can now provide convenient, secure, and reliable connections between specialists, primary care physicians, and patients anytime and anywhere. In a true patient–centred model of care, technology will simply bring people separated by distance together to provide care, education, and support. The effectiveness of such connections will depend on the working relationships of the people being connected. We believe that the evaluation of telemedicine programs in this province should consist of measures that matter—health outcomes, the patient experience, and costs—"The Triple Aim".[10] For this to be most useful, similar evaluations of current urban practice will be needed.

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Moving gene therapies from the lab to the hospital bed: The adeno-associated virus as a promising gene therapy vector to treat disease

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Abstract

Gene therapy is a treatment method repairing mutated or deleted genes to correct genetic disorders. With many monogenic diseases lacking effective therapeutic approaches, gene therapy offers an exciting avenue to resolve the underlying genetic abnormality. Further, gene therapy could also address complex multifactorial diseases by targeting a critical pathway. Regardless of the therapeutic goal, an important factor to consider is the challenging step of efficiently and precisely delivering genes of interest to cells of interest. These vectors must ideally evade immune response as they infect cells of interest and be able to infect a wide spectrum of target cells. One such vector that has demonstrated much promise is the adeno-associated virus (AAV). The AAV was discovered over 50 years ago and has since been studied extensively for the treatment of many diseases. Since the first AAV clinical trial started in 1996 for the treatment of cystic fibrosis, hundreds of trials have examined AAV-based therapies for the treatment of hemophilia, rheumatoid arthritis, Duchenne's muscular dystrophy, Leber's congenital amaurosis, lipoprotein lipase deficiency, and many other genetic disorders. With the first AAV drug approved in the last four years, we may soon gain insight into the feasibility of this type of gene therapy product. This review discusses the basic structure and design of AAV vectors and reviews recent advances in AAV technology enabling these therapies to reach the clinic.

There are currently over six hundred clinical trials registered in the United States National Institutes of Health studying "Gene Therapy."[1] Broadly speaking, gene therapy is a treatment method to replace or repair mutated or deleted genes to correct genetic disorders (e.g., repairing mutations in clotting factors to correct hemophilia). Importantly, the possibilities for gene therapy extend to complex pathologies such as autoimmune disorders by providing genes to suppress local autoimmune attack,[2] or to selectively target cancer cells to suppress oncogenesis or hone immune cells.[3] With these seemingly endless therapeutic possibilities, it is important to consider the delivery methods of gene therapy. These vectors must ideally act as an undetected "Trojan Horse," capable of evading all immune reaction and selectively targeting only cells of interest. The vector that has come closest to meeting these criteria, is the adeno-associated virus (AAV).

The adeno–associated virus

The AAV was first discovered in 1965 in Pittsburgh.[4] Though initially thought of as an impurity of the adenovirus preparation, it was discovered that it was a parvovirus that was thereafter described as "adeno-associated." Since then, many unique features have been discovered that make the AAV highly suited to use as a clinical gene therapy vector. First and foremost, the AAV is considered non-pathogenic as it causes little to no immune response.[5] In fact, most of the population has been infected by wild-type AAV without any obvious or common symptoms.[6] Second, there are many AAV serotypes with unique tropism for a variety of tissues[7] and rational capsid modifications can result in improved selectivity and even change its immunological profile.[8] Third, the AAV's structure suits a gene therapy vector as a non-enveloped single-stranded DNA virus. The wild-type genome encodes replication and capsid proteins and is flanked by two inverted terminal repeats (ITRs).[9] Though the wild-type single-stranded AAV takes upwards of four months to initiate gene expression,[10] modification to remove a component of the 3' ITR can allow packaging as a self-complementary double-stranded virus capable of initiating gene expression less than one week after infection.[11,12] This does come at the expense of limiting packaging to ~2.5 kb, though as only the ITR is necessary for packaging, the remaining ~2.3 kb can be engineered with a suitable promoter and gene of interest. Finally, the AAV genome structure is highly stable, enabling prolonged transgene expression with reports of residual expression up to four years after therapy in a human patient.[13] Taken together, non-pathogenicity and fast yet prolonged expression have combined to result in the AAV becoming one of the most studied gene therapy vectors.

For AAV to be viable in the clinic, another important consideration is its manufacture. Most importantly, the AAV is replication-deficient and is hence sub-classified as a "dependovirus". This means that the AAV depends on the functions of a helper virus, such as an adenovirus or herpesvirus to replicate in a host mammalian cell.[14] Clinically, this means that the AAV cannot autonomously replicate in a host but also means that large-scale manufacturing is challenging and costly. Production of a pure recombinant AAV lacking any wild-type virus impurities and produced without the use of adenovirus (hence avoiding adenovirus impurities), has conventionally been done by a triple plasmid transfection system.[15] Adherent HEK293 cells are transfected with the construct of interest, a plasmid containing the AAV-specific replication and capsid genes, and a third plasmid expressing the essential adenovirus genes.[7] Importantly, the use of adherent cell cultures requiring serum-supplemented media greatly limits production of virus meeting current acceptable manufacturing protocols,[16] but there are other technologies,[17] and some recent advances have allowed serum-free suspension cultures, thereby improving production efficiency.[18] With these promising advancements, scalability at bearable cost continues to improve and lead to greater opportunity for an AAV therapy to reach patients globally.

Despite these successes, as the AAV has gained greater attention, researchers have begun to discover previously unappreciated risks and

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challenges to using the AAV itself. To date, there have been limited reports of an association between AAV infection and spontaneous abortion.[19] Additionally, a recent paper suggested that a certain serotype of AAV (AAV2) may be linked to hepatocellular carcinoma.[20] Importantly, these findings have since been heavily challenged,[21-23] though given the frequent presence of the wild-type 3' ITR in these cancers, the wild-type AAV may pose a small risk.[22] This may not be a problem for modified AAV vectors since clinical AAVs use only 145 bp (the 5' ITR) from the wild-type genome.

Alongside potential pathogenicity, research has found the presence of AAV–neutralizing antibodies in humans.[24] This was unexpected based on animal preclinical studies but may explain the acute liver damage resulting in short-term elevation of liver enzymes following liver AAV infection.[25] Nonetheless, there are many strategies to avoid this roadblock such as improving vector efficiency to reduce doses needed or transient immune suppression before AAV administration.[26] The research community has seen many successful clinical trials for many monogenic diseases—more than 120 published clinical trials using AAV vectors have failed to find severe side effects.

Clinical research using the AAV

In 1996, the first AAV reached the clinic in a phase I clinical trial for the treatment of the monogenic disease cystic fibrosis.[27] Since then, AAVs have been studied to treat hemophilia B, rheumatoid arthritis, Duchenne's muscular dystrophy, Leber's congenital amaurosis, lipoprotein lipase deficiency, and many other diseases.[28] Among the most promising research includes treatment for hemophilia B, a disease characterized by impaired blood clotting due to insufficient factor IX.[25] In ongoing phase I/II clinical trials, there have been reports of patients being free of multiple weekly factor IX infusions for over a year after a single AAV injection, with these patients maintaining factor IX levels sufficient for normal clotting times comparable to healthy counterparts.[29] Another disease with abundant promising AAV clinical research is Leber's congenital amaurosis, which causes childhood blindness. Early clinical trials showed improved visual acuity just weeks after replacement of the mutated gene (RPE65) by AAV.[30] Since, this work has advanced to a stage III clinical trial[31] and the biotech company, Spark Therapeutics, has released incredible findings: having treated 29 patients, all demonstrate profound improvements in light sensitivity and eye mobility and Spark Therapeutics report that there have been no "product-related serious adverse events."[32] Through all these promising findings on AAV-based therapies, the trailblazer into clinical approval is treatment for congenital metabolic disorder lipoprotein lipase deficiency (LPLD) that reached clinical approval in Europe just four years ago.

Alipogene tiparvovec (Glybera®) was first recommended for approval in 2012.[33] This was the result of a long process requiring four reviews by the Committee on Human Medicinal Products.[34] Though large datasets of clinical outcomes are yet to be released, a few key lessons have already been learned from the first AAV approved therapy. First, much like Glybera®, future gene therapies will also need to face the challenge of identifying a sufficient population for a phase III clinical trial for rare diseases and the associated struggles when taking small phase III trials to review boards for final clinical approval. Furthermore, the cost associated with multiple appeals for drug administrations is often prohibitive and was only successful for Glybera® thanks to private donors. Even after approval, health care systems will be faced with the extreme cost associated with such a therapy—after much speculation and many estimates,[35] the final cost landed on $1.4 million USD for the one–time treatment.[36] But for a disease with severe cost in quality and quantity of life without an effective treatment, an immediately expensive gene therapy product may in fact be cost-effective and bearable to users with extended payment plans.[37]

Conclusion

Gene therapy is a promising avenue for clinical research to treat both rare monogenic diseases and common multifactorial diseases. In this review, the promising characteristics of the AAV as a gene therapy vector have been discussed, alongside important details of virus production. Clinicians are now able to prescribe AAV-based therapies and could become involved in the development of future therapies. An understanding of the limitations and risks associated with current production technologies provides a realistic perspective on future development and use of these medications for Canadian patients and the Canadian healthcare system as a whole.

With the first AAV-based drug approved for clinical use in Europe, the challenging path to the clinic has been clarified. By having a realistic perspective on the clinical challenges facing AAV-based therapies from manufacturing to immunology, it is hoped that future research will consider that to be acceptable to health agencies and public health providers, AAV treatments will need to offer major improvements in quantity and quality of life for patients, and cost-saving outcomes for private and public healthcare. With this consideration, it is possible that AAV gene therapies could one day be part of the standard of care for rare and common diseases. Promising results from AAV clinical trials treating Leber's congenital amaurosis and hemophilia make it likely that Canadian physicians need to be prepared to evaluate AAV therapies as a treatment option for their patients in the not-so-distant future.

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Social support: A useful tool in the management of psychotic disorders

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Abstract

Psychotic disorders are a major source of disability worldwide. Individuals living with psychotic disorders may be particularly vulnerable to low social support and reduced social support networks. Social support interventions represent a promising method to encourage functional recovery and improve quality of life for this population. Understanding the specific changes in social support perception, satisfaction, network size, and structure, throughout the course of psychotic illnesses, and how these factors interact with psychotic symptoms, is therefore essential to creating effective social support interventions for this population. Both family and peer–based social support interventions can be used clinically to improve social support, self–efficacy, and quality of life. Friends–based interventions may be a more natural way to promote existing relationships, and should be explored through randomized controlled trials (RCTs). Implementation, monitoring, and adherence to social support programs represent critical barriers to the success of these interventions. We suggest that the most effective social support interventions for this population should be individualized, closely monitored, and perceived as valuable to be effective for individuals living with psychosis.

Introduction

Schizophrenia accounts for 7.4% of all disability–adjusted life years (DALYs) caused by mental illness and substance use disorders worldwide.[1] Moreover, the proportion of DALYs attributable to schizophrenia rises in young adulthood and peaks between ages 25-50, a period in which individuals make substantial contributions to society.[1] Schizophrenia is classified as a psychotic disorder, along with schizoaffective disorder, delusional disorder, and schizophreniform disorder; all are characterized by detachment from reality.[2] Despite treatment advances, including the development of second–generation antipsychotics reporting fewer extrapyramidal side effects, treatment initiation and adherence remain important barriers to preventing relapse and improving quality of life for individuals living with psychotic disorders.[3-8] Social support, especially in the context of family support, has been consistently recognized as a tool to improve health outcomes, but its use in the context of psychosis is relatively underexplored.[9-11] As such, there is a need for novel interventions in this field.

The World Health Organization has recognized social support as an important contributor to physical and mental health.[12] Social support is especially important for those experiencing psychosis, as it has been demonstrated that those with psychotic disorders report lower social support than control groups.[10] Social support and social networks begin to decrease prior to the onset of first episode psychosis.[13] While the definition of social support varies between studies, it can be viewed as "the perception or experience that one is loved and cared for by others, esteemed and valued, and part of a social network of mutual assistance and obligations."[14] Social support can be categorized into specific forms, including emotional support, tangible support, companionship support, and informational support (Table 1).[13] Social support can also be described as perceived support, including the perceived availability and adequacy of supportive relationships, or enacted support, consisting of the supportive behaviours themselves.[15,16] Here, we provide a narrative overview of literature on the relationship between social support and psychotic disorders, as well as the role of social support interventions for psychotic disorders in a clinical setting.

Methods

Relevant literature was selected by searching Ovid MEDLINE using the MeSH headings "social support" AND "psychotic disorders" as well as searching Google Scholar with combinations of the keywords "social support", "psychosis", and "intervention". Additional articles were found by searching the articles referenced by those identified in the initial search.

Results

Social support for individuals living with psychotic disorders

Features of certain psychotic disorders, including both negative and positive symptoms, may cause individuals to withdraw from social networks or create difficulty in maintaining relationships.[17,18] Therefore, individuals living with psychotic disorders may be vulnerable to low social support or reduced network size. Depleted social networks may result in less resilience during crisis, thus potentially contributing to a cycle of worsening psychotic symptoms and social withdrawal.[13] While it is well documented that those living with psychotic disorders generally have smaller social networks than control groups,[13] more subtle differences in support structure and perception of support may also provide important insight into the mechanism by which psychosis symptom severity and social support interact.

In addition to smaller social networks, individuals experiencing first–episode psychosis have more highly interconnected social networks composed of a greater proportion of family members, and

Table 1 | Types of social support.[12]

Type of Social Support	Description
Emotional support	Providing emotional care
Tangible support	Consisting of goods, services, and financial assistance
Companionship support	Providing a sense of belonging
Informational support	Supplying knowledge and advice

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report lower levels of perceived social support as well as less time spent with network members compared to control groups.[19-21] Macdonald et al.[22] showed that individuals with early psychosis did not differ from controls in amount of perceived social support, number of family members, reciprocal relationships, or acquaintances; however, those experiencing psychosis reported smaller networks, a higher probability of service providers as network members, and fewer network members to rely on during crisis compared with closely matched controls.[22] These differences in social networks may translate into meaningful differences in quality of life and outcomes for individuals living with psychotic disorders, and should be considered as a potential target for treatment.

Recent studies have examined associations between social support and three factors that are associated with the course of psychotic disorders: symptom severity and recovery, duration of untreated psychosis (DUP), and medication adherence.[23-27] Poor perceived social support, loneliness, and absence of a confidant have been correlated with increased psychosis and depressive symptom severity.[26] Participants' satisfaction with social support was more strongly correlated with symptom severity than perceived availability of support, indicating that merely having support available is not enough. Quality and extent of relationships for those living with psychotic disorders may be associated with improved functional outcomes, such as returning to full–time occupation.[27] Appropriate social support may therefore play a role in both the amelioration of symptoms and encouragement toward an individual's recovery goals.

For individuals experiencing their first episode of psychosis, a shorter DUP—the length of time that passes between emergence of symptoms and initiation of treatment—is a modifiable factor associated with better treatment outcomes.[24,28,29] Several studies have shown that poor social support is associated with longer DUP.[25,30] However, when social support was further divided into close contacts (i.e., confidants, close relatives, and cohabiting contacts) and diffuse contacts (i.e., work or school associates, neighbours, and clubs or organizations), only the quality of diffuse social support was significantly correlated with DUP.[24] In keeping with other research, this suggests that considering both quality and structure of social networks, and not simply size, may be very relevant to modifying the DUP, and thus clinical outcomes.[19]

Furthermore, perceived family support has been shown to be positively correlated with adequate medication adherence in the months following a first episode of psychosis, defined as taking more than 75% of antipsychotic medication doses.[23,31] However, one study showed that an increase in social support was modestly associated with a decrease in medication adherence when followed over time.[23] The authors suggest that individuals with higher levels of perceived social support may feel better overall, potentially resulting in a decreased perceived need for medication, which may account for the reduced adherence.[23] Moreover, the positive association between social support and medication adherence may only be seen if social support is provided consistently.[23] This research highlights the complexity of the interaction between social support and treatment adherence over time.

Interpretation of these correlational results, however, is made difficult by interactions between factors, and deciphering the directionality of the effect is difficult. For example, more severe symptoms at initial presentation may account for both the decreased social support and poor outcomes, through a cycle of increased social withdrawal and disruption of relationships.[17,18] Researchers have tried to mitigate these potential confounds by measuring self–reported social support before the onset of prodromal symptoms,[25] but these reports are limited by recall bias. Despite these limitations, there is potential for social support to encourage treatment adherence and support functional recovery. It is essential that social support interventions be appropriate and perceived as valuable to the patient, as well as monitored over time, in order to be effective.

Clinical use of social support interventions for psychotic disorders

Several approaches have been taken to incorporate social support into the treatment of psychotic disorders, most notably family and peer support. Since Brown et al.'s early research demonstrating that individuals with schizophrenia living within tense family environments are predisposed to relapse,[32] family–based interventions have become an important target in schizophrenia treatment. Multiple meta–analyses and reviews have established that family interventions are effective in reducing relapse and re–hospitalization and increasing medication adherence.[33-37] While there is variation amongst these interventions, many include a combination of family education and family therapy with the overall goal of improving family atmosphere.[34]

While family–based interventions are more widely used, peer support interventions represent a promising strategy to encourage social connectivity and support for those living with psychosis.[38,39] Peer support is based on the concept that individuals suffering from a common disease can provide one another with emotional support, appraisal support, informational support, and hope.[38] In the first RCT examining the role of minimally guided peer support groups for people living with psychosis, those assigned to the support group reported less negative symptoms and less associated distress.[38] Only those that attended more than half of the sessions, however, showed significant improvements in social support, self–efficacy, and quality of life, compared to controls.[40] This finding was replicated by a later study using minimally guided peer support groups for people with a history of psychosis, which again reported that only those that attended more sessions scored significantly higher on quality of life measures.[41] In a study in which individuals were randomly assigned to a one–on–one peer mentor or usual–care control group, those in the peer mentor group reported significantly fewer hospital readmissions and shorter stays.[40] An important drawback to this intervention is that over one–third of participants in the treatment group did not have contact with their peer mentor.[42]

Initiation and adherence to peer support groups are critical barriers to the effectiveness of this type of intervention. As described earlier in this review, social withdrawal may occur with features of certain psychotic disorders. Those that have more intact social support to begin with may also be those most willing to engage in peer support groups. In turn, these interventions may fail to benefit the most isolated individuals. To maximize the benefits of peer support groups, participants should evaluate interventions to ensure they are perceived as valuable and that the intervention targets each individual's social support goals. A recent narrative review by Harrop et al. suggest that "friends–based interventions", aimed at supporting existing friendships and romantic relationships, may represent a more effective way to maintain the social networks of those living with psychosis.[39] More large–scale RCT trials are necessary to determine the effectiveness of "friends–based interventions". Although RCT data demonstrate that peer support interventions may represent a promising strategy to

enhance the social support networks of those living with psychosis, participant engagement represents a barrier to achieving significant improvement in outcomes. In fact, the most effective interventions should be individualized and may combine family–based, peer–based, and friends–based interventions to support existing networks while providing additional support where it is necessary.

Discussion

This narrative review of the available literature on social support interventions in the treatment of psychotic disorders suggests that these tools are useful in modifying clinical outcomes. The methods used to survey the breadth of social support in this population were not systematic, and thus, we are unable to comment on the magnitude of the effect or adequately grade the quality of the available evidence.

Conclusion

Literature has demonstrated the association between social support, including family support, extended social networks, and presence of a confidant, with aspects of psychotic disorders such as treatment initiation and adherence, symptom severity, and real–world functioning.[23-27] While family–based interventions to improve support have demonstrated success and are integrated into various best–practice guidelines, the success of peer support–based programs appears to be affected by the ability of an individual to engage and maintain participation.[43,44] This aligns with previous findings that merely having support available is not beneficial if the support is not perceived as needed, valuable, or satisfactory to the individual. Monitoring aspects of social support, such as perception, satisfaction and need, as well as network structure, before and during the provision of social support interventions, may improve their effectiveness for individuals living with psychosis.

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Advances in genetic sequencing and genomics in the detection and analyses of genetic variants in neurological disorders: A review

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Abstract

With recent advances in genetics and genomic sequencing, it has become possible to screen for genetic variants and polymorphisms in the human genome that contribute to heritable forms of neurological diseases. With an increasing proportion of the population aged 55 years and older, there will be an increased incidence of neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD). That will mean an increasing burden on our healthcare system and an increasing need for resources and expertise to treat and manage these diseases. In addition, multiple sclerosis (MS) is the most common neurological disorder in young adults, and the prevalence of MS has increased over the last few decades, with MS incidence and prevalence in British Columbia among the highest worldwide. This review will: 1) Highlight recent advances in genetic sequencing and genomics that have allowed for improved detection, characterization, and analyses of genetic variants linked to cases of AD, PD, and MS and 2) Address some considerations when using genetic testing to detect and analyze genetic variants linked to cases of neurological diseases.

Introduction

Improvements in genetic sequencing and genomics have allowed researchers and geneticists to identify genetic variants in the human genome that are associated with an increased risk of developing neurological disorders such as AD, PD, and MS. Genetic variants and polymorphisms associated with an increased risk of developing neurological disorders tend to be more prevalent in families with a history of multiple relatives suffering from a disease. Studying families with rare genetic variants that increase the risk of neurological disorders allows researchers to investigate the effects of genetic variants on the likelihood of developing a disease as compared to the general population. In the past few years, the invention of massively parallel sequencing technologies have allowed scientists to study the causes of a disease at a molecular level while using advanced computational techniques to filter and analyze large amounts of genomic data to find genetic information that relates to an individual's health and the pathophysiology of disease processes.[1] Researchers have dubbed massively parallel sequencing techniques as "-omics" technologies, which have allowed researchers to study the structure, function, and interactions of biomolecules making up cells.[1] Examples of massively parallel sequencing techniques include next generation sequencing (NGS) for detecting DNA variants involved in the development of disease and RNA sequencing for transcriptome analysis and studying the roles of non–coding RNA in disease pathogenesis.[1] The full list of sequencing technologies available for studying the molecular mechanisms of disease is extensive, but it is important to note that NGS is already being used to develop more sensitive diagnostic tools and to identify new molecular targets that could potentially be used in the development of therapeutics.

Advances in genomics for diagnosing early onset Alzheimer's disease

Currently, AD can be confirmed only with a post–mortem autopsy and is characterized by neuropathology, such as extracellular β–amyloid plaques formed by insoluble Aβ-42 peptides and intracellular Neurofibrillary Tangles (NFTs) that are composed of hyper–phosphorylated Tau proteins.[2,3] During the course of AD, neurodegeneration triggered by Aβ-42 peptides and NFTs occurs with extensive loss of grey matter in the hippocampus, the temporal lobes, and the neocortex.[2,3] These pathological processes lead to the characteristic behavioural symptoms seen in AD, which include cognitive decline, memory loss, and impairments in consolidation of new memories.[2,3] In a recent study of individuals with early onset AD (family history of AD at <65 years) or very early onset AD (≤55 years), researchers used exome sequencing to study all coding regions of the genome to look for genetic variants associated with an increased risk of AD.[4] Twenty–nine genetic variants potentially involved in the development of early onset AD were identified, while only one gene, Protein Tyrosine Kinase Binding Protein (TYROBP), was selected for genetic and functional validation.[4]

TYROBP was further studied because it is known to be upregulated in AD brain tissue and was shown to be involved in the pathogenesis of late onset AD.[5,6] TYROBP is a binding partner of Triggering Receptor Expressed On Myeloid Cells 2 (TREM2), which is itself a genetic risk factor for AD.[7,8] In the central nervous system (CNS), TYROBP is expressed in microglia, where it binds to ligands such as TREM2, which leads to a cell signaling cascade triggering proinflammatory responses and phagocytosis of cellular debris by microglia.[9,10] TYROBP is also thought to be involved in Amyloid-β (Aβ) turnover, which is significant because TYROBP genetic variants implicated in AD could alter normal microglia functions, such as the clearance and phagocytosis of abnormal proteins in the maintenance of tissue homeostasis in the CNS.[6] Studies using advanced genetic sequencing techniques have allowed researchers to understand more about the neuropathology and pathogenesis of AD, as well as to identify genetic variants linked to rare forms of early onset AD.[4,6]

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Genetic sequencing and hereditary forms of Parkinson's disease

Discovery of genetic variants conferring an increased risk of developing PD has come from over 25 years of research on the etiology and pathogenesis of the disease. In a paper published in 1997, a genetic mutation in the α-synuclein gene that caused an autosomal dominant pattern of parkinsonism was identified in a large family of Italian descent.[11-13] Alpha–synuclein is a presynaptic protein found in CNS neurons that is a major constituent of Lewy bodies (the major neuropathological hallmark of PD and dementia with Lewy bodies) and can be found in dopaminergic neurons of the substantia nigra pars compacta, which undergo neurodegeneration in cases of idiopathic PD.[14] Family members who possessed the α–synuclein mutation manifested the disease 85% of the time and presented with typical clinical symptoms of PD, but had an earlier age of disease onset as compared with idiopathic PD.[11,12]

More recently, new genetic variants have been identified as causes of familial PD, with signs and symptoms similar to idiopathic PD. Leucine–rich repeat kinase 2 (LRRK2) gene mutations were linked to autosomal dominant parkinsonism that presented with α–synuclein neuropathology.[15,16] In a 2008 study, it was determined that six genetic mutations in LRRK2 were pathogenic in the development of PD.[14] Of these, the frequency of the more common Gly2019Ser mutation was estimated to be present in 1% of idiopathic PD patients, as compared with 4% of patients with a heritable form of PD.[15] The risk of developing PD for those who are carriers of the LRRK2 Gly2019Ser mutation increases steadily with age.[15] Patients with mutations in LRRK2 on average had a shorter disease duration and slightly earlier onset of PD symptoms as compared with patients with idiopathic PD.[15]

In addition to improving the ability to discover hereditary forms of PD, which are estimated to contribute to 15% of total PD cases, genetic sequencing has shown that LRRK2 Gly2019Ser mutation carriers have a unique clinical presentation that could aid in the diagnosis and management of this subtype of parkinsonism.[15,17] In a large study of PD patients with LRRK2 Gly2019Ser mutations, subjects presented with bradykinesia, asymmetrical tremors, and muscle rigidity, which responded to dopamine replacement therapy and functional neurosurgery, with tremor symptoms and abduction–adduction leg tremor being more common in comparison to idiopathic PD subjects.[15] Interestingly, those PD patients with LRRK2 Gly2019Ser mutations had a lower risk of developing non–motor symptoms, such as cognitive impairment and hyposmia, as compared with patients with idiopathic PD.[15]

In a clinical genetics study published in 2016, researchers found that genetic variability in the dynamin-3 (DNM3) gene modified the age of onset for LRRK2 Gly2019Ser parkinsonism.[18] Using genome-wide linkage analysis and whole genome sequencing (WGS), researchers were able to identify genetic associations that can affect the genetic penetrance and clinical phenotypes of a hereditary form of PD.[18]

Identifying genetic variants associated with multiple sclerosis

In recent years, it has become apparent that genetic predisposition plays an important role in the risk of developing MS as well. MS is a progressive inflammatory and demyelinating disease of the CNS and is the most common neurological disorder in young adults, affecting 100,000 Canadians and 2.5 million people worldwide.[19] MS can be separated into several subtypes based on clinical features and disease phenotypes. The most common pathological feature of MS is the presence of focal lesions or plaques in the white matter (WM) of the CNS that can be visualized and characterized by histology or MRI techniques.[20,21]

Recent studies have identified both genetic variants and biomarkers in the cerebrospinal fluid (CSF) of MS patients that could be used to predict symptom severity and clinical course in the progression of MS.[22] In one study, researchers recruited a cohort of 127 patients who had recently experienced their first demyelinating episode, and subjects were genotyped to determine if they possessed MS–associated single nucleotide polymorphisms (SNPs) that could predict the clinical course of disease.[23] Nine SNPs were identified that correlated with conversion to MS and/or episodes of MS relapse; two SNPs were located in Human Leukocyte Antigen (HLA) genes, and seven SNPs were in non–HLA genes.[23]

A recent paper also identified the first potential pathogenic mutation for MS in the Nuclear Receptor NR1H3 gene in seven patients with MS from two unrelated families with multiple cases of MS diagnosed in family members.[24] Individuals from the two families presenting with MS had severe and progressive forms of the disease, with an average age of onset of 34 years.[24] Exome sequencing of the two families discovered the presence of a p.Arg415Gln amino acid substitution in the NR1H3 gene, with the mutant form of NR1H3 inhibiting the heterodimerization of LXRA (the gene product of NR1H3; Liver X receptor-α), leading to alterations in gene transcription, which could be involved in the pathogenesis of some forms of MS.[24]

Considerations and conclusion

While genetic sequencing and genomics have improved the detection of rare genetic variants linked to neurological disorders, there are drawbacks to the use of whole genome sequencing (WGS) in identifying and characterizing diseases such as AD, PD, and MS. Drawbacks include detection of false positive genetic variants and increased false discovery rates (FDR) of genetic variants when using WGS. In a recent Japanese study, geneticists used WGS to identify de novo mutations in the human genome.[25] Discovery of false positive results and the FDR for genetic variants is affected by the choice of genomics platform and the statistical analyses used to determine the significance threshold in the detection of genetic variants potentially linked to a disease.[25] When identifying novel SNPs using whole genome sequencing (WGS) in the human genome with the error rate set at 0.001%, researchers found 30,000 false positive results across the entire human genome.[25]

More recently, a genetic study has demonstrated the use of WGS for increasing diagnostic utility and improving clinical management of pediatric patients diagnosed with neurological disorders or congenital abnormalities.[26] In the study, authors compared the use of WGS and chromosome microarray analysis (current standard genetic testing) in identifying disease-causing genetic variants in 100 children referred to the pediatrics genetic service.[26] The authors found that WGS identified genetic variants meeting clinical diagnostic criteria in 34% of cases, as compared with 8% of cases using standard genetic testing.[26] Other studies showed that WGS identified genetic variants meeting clinical diagnostic criteria in 25% of patients with neurological and congenital disorders.[27,28] However, the percentage of cases in which WGS can identify a disease-causing genetic variant is still fairly low, and the cost of sequencing a single patient's genome is expensive (estimated to be $3,000 per patient in some recent studies).[26] It is important to highlight

the fact that many neurological diseases are caused by the interaction of environmental factors with genetic variants at multiple different genetic loci and that each gene variant usually conveys only a small risk in the development of a neurological disease.[29] Therefore, genetic testing might currently only be useful in those patients with de novo mutations leading to development of disease or in those individuals with a strong family history of a neurological disease.

This review provides a snapshot of emerging clinical research using genetic sequencing and genomics techniques to identify pathogenic gene variants and mutations in neurological diseases such as AD, PD, and MS. While genetic sequencing has provided numerous insights into the etiology, pathogenesis, and molecular mechanisms of neurological disorders, there are several considerations one must take into account when using genomics to detect pathogenic genetic variants in patients. All patients should be offered pre-test and post-test genetic counseling about the risks and benefits of receiving testing for detecting genetic variants in determining risk and diagnosis of neurological diseases. Physicians should clearly explain the sensitivity and specificity of the genetic techniques and explain the relative risk of developing a disease if the patient is a carrier for a given gene variant. Implications of genetic testing should also be considered for a patient's family members, as pathogenic gene variants tend to cluster in families and family members of an individual identified as a carrier. A patient's family members should also be offered genetic counseling and genetic testing to determine if they are carriers.

Finally, the decision to conduct genetic testing for a patient should take into account the frequency of the mutation in the population and whether the patient is in a high–risk group for carrying a particular pathogenic mutation.[15] Presymptomatic patients and patients with a neurological disease should be advised that the main benefits of testing are to improve the accuracy of a diagnosis or to determine the relative risk of developing a disease if an individual is a mutation carrier.[15] In many cases, testing will not influence therapeutic options for a patient, but it can influence patient-centered care for the management of a disease, which is important in allowing individuals to make informed choices about their healthcare. For these reasons, it is important for researchers, healthcare providers, and ethicists to develop best practice guidelines for how personalized genetic information should be used to maximize the benefits and minimize the risks for the physical and mental wellbeing of patients and their families.

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Grandpal Penpals: A qualitative study of a social program on senior quality of life in residential care facilities

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Abstract

Objectives Grandpal Penpals (GP) is a unique community program that connects seniors living in residential care with elementary school students through pen pal letter writing and visits. A common belief is that seniors have a lower quality of life in residential care facilities. We qualitatively explored how this program related to the senior participants' quality of life in the domains of motivation, activities, relationships, and autonomy.

Methods Among participants in the GP program, seniors who were sufficiently cognitively intact were chosen to participate in our study. In–person interviews were conducted with participants at the beginning and at the end of the program to determine major themes.

Results Four major themes were identified: 1) GP strengthened the participants' pre–existing motivations, 2) participants perceived social programs like GP to be enjoyable and beneficial while actively involved, 3) most participants found that GP did not affect their interpersonal relationships, and 4) GP did not affect the participants' self–perceived level of autonomy.

Conclusions While participants greatly enjoyed GP, they perceived little relation of the program to their overall quality of life. Our research suggests that other highly engaging, goal–oriented, long–term social programs with increased senior–senior or senior–family interaction may be of greater relevance and benefit.

Abbreviations GP, Grandpal Penpals; QoL, Quality of Life; ADLs, activities of daily living; P#, participant identification number (randomly assigned to maintain participant anonymity)

Introduction

By 2036, approximately 25% of the Canadian population will be over 65 years old.[1] With increased age and chronic illness, the capacity to carry out activities of daily living (ADLs) is compromised due to deterioration of overall health.[2,3] In 2014, almost 33% of Canadian seniors were living in full service residential care facilities[1]—facilities which care for seniors unable to independently perform ADLs.

Quality of life (QoL) in residential care facilities is an active area of research with literature showing that increased QoL can improve survival and decrease morbidity.[4] As defined by the WHO, QoL is an individual's perception of life in relation to their goals, expectations, standards, and concerns.[5] These positive domains are common focuses for public health promotion programs,[6] and may include: empowerment to live, functional competence, social relationships, meaningful activities outside ADLs, and global motivation.[6,7]

Grandpal Penpals (GP) is a novel 8–month community program that connects seniors living in residential care facilities with elementary school students through monthly letter writing and social visits. Recreational staff at the residential facilities help senior participants read and respond to letters. Social visits, organized around themes of "family", "fitness", and "music", take place at either the residential facilities or elementary schools, and involve activities such as games, crafts, and singing. For four years, GP has been established in multiple Vancouver–based residential care facilities and elementary schools. Though it has been verbally received well by past participants, its relation to participants' QoL has yet to be evaluated.

Throughout the 2015-2016 program, senior participants were individually interviewed to discuss their QoL in context of four relevant domains: autonomy, meaningful activities, relationships, and motivation. This article shares recurrent themes regarding this program's relation to QoL in residential care facilities.

Materials and Methods

Ethics approval

Ethics approval for this project was obtained from the University of British Columbia Behavioural Research Ethics Board (H15-02255). All participants provided informed verbal consent, with witness signatures by residential facility staff. No participants received any reward for involvement or penalty for withdrawing.

We hereby declare that for research involving human subjects, procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Recruitment of participants

English speaking seniors residing in Arbutus Care Centre and Point Grey Private Hospital who agreed to participate in GP were eligible. Care facility recreational staff identified potentially eligible individuals who met inclusion criteria. Seniors who were not deemed competent to provide informed consent were excluded, such as those with severe dementia who were unable to understand the purpose, operation, benefits, and risks of the program. The participants' cognitive statuses were not formally assessed, as no clear Mini-Mental State Exam or Montreal Cognitive Assessment Tool score would be representative of the participants' abilities to partake in the program and comment on their experience.

Interview question design

With numerous measurement tools, QoL research has not always been consistent. Furthermore, no validated qualitative instruments exist. Definitions and terminology from various studies[6,7] were used to design open–ended questions to address the four most pertinent QoL domains: autonomy, motivation, activities, and relationships (Table 1).

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Table 1 | Pre- and post-program interview questions.

Quality of life domain	Pre-program questions	Post-program questions
Autonomy: Empowerment refers to one's individual sense of self-determination and autonomy.	When do you feel like you have the power to make decisions that you feel are best suited for you? When do you not?	How has your participation in the program changed your power to make decisions that you feel are best suited for you?
Autonomy: Functional competence is defined to mean that, within their physical or cognitive abilities, residents were as independent as they wanted to be.	Within your physical and cognitive abilities, do you feel as independent as you would like to be? What does independence mean to you?	How has your participation in the program changed your level of independence?
Relationships: is defined as any relationship that the resident finds meaningful.	Can you describe your close relationships and the people you can confide in (i.e. other residents, family, staff, visitors)? Can you elaborate on what a meaningful relationship to you entails (i.e. physical, emotional, verbal, point of view)?	How has your participation in the program changed your relationships and people you can confide in (i.e. other residents, family, staff, visitors)?
Meaningful activity: encompasses activities outside of activities of daily living that gives individuals a sense of enjoyment.	What sort of activities are you participating in that give you enjoyment and are meaningful to you? Can you elaborate on what a meaningful activity means to you?	How has your participation in the program changed the activities you are participating in? Are you participating in more or less activities that give you sense of enjoyment and are meaningful to you?
Global motivation	What motivates you to take care of yourself (i.e. activities of daily living, hobbies)?	How has your participation in the program changed your motivations to take care of yourself?

Data collection and interview process

Prior to data collection, all researchers practiced interviewing peers with live feedback until no major discrepancies were noted between researchers. The training focused on asking neutral, non–leading, open–ended questions. Both pre–program and post–program semi–structured interviews were conducted by familiar researchers in quiet spaces of the residential facility to maintain participant comfort and good rapport. Interviewers obtained informed verbal consent prior to each interview, but they were otherwise unknown to the participants. Interviewer bias was mitigated by the use of five standardized, open–ended questions to address the four quality–of–life domains: autonomy, motivation, activities, and relationships (Table 1). The length of interviews ranged from 15 to 60 minutes.

All interviews were audio–recorded, transcribed, and assigned file numbers; no identifying information was attached. Researchers took note of affect and body language throughout the interview which, during transcription, provided qualitative context to responses. To further reduce interviewer bias, no participant was interviewed twice by the same researcher.

Data analysis

Each transcript was divided into four sections, corresponding to the four QoL domains. Within each domain, the transcripts were examined by at least two researchers using inductive coding. The inductive codes were then organized into categories. Categories that contained codes identified in at least half of the interviews were regarded as major themes. All researchers reviewed the final themes to ensure interpretation accuracy and consistency.

Results

Demographics

Between October 2015 and May 2016, eight participants took part in the study, four from Arbutus Care Centre and four from Point Grey Private Hospital. Of these, five were female and three were male. The participants were 63 to 95 years old, with an average age of 85 years. At the time of the final interview, the participants had lived at their current accommodations for 9 to 23 months, with an average length of stay of 14 months. Two participants from Point Grey Private Hospital were unable to follow up at the second interview; one had passed away, and one had transferred facilities. Full demographic information is provided in Table 2.

We assessed the relationship of GP to four QoL domains: motivation, activities, relationships and autonomy. Major themes identified in each domain include: 1) GP strengthened the participants' pre–existing motivations, 2) participants perceived social programs like GP to be enjoyable and beneficial while actively involved, 3) most participants found that GP did not affect their interpersonal relationships, and 4) GP did not affect the participants' self–perceived level of autonomy.

Motivation

In the pre–program interviews, the participants cited various global motivations, including pleasurable hobbies, valuable relationships, maintaining a presentable appearance, and a general passion for life. In the post–program interviews, three out of six participants stated they felt increased daily motivation. Of these, two were inspired to interact with others, and one was motivated to do rehabilitation exercises to look healthier and more youthful. It is notable that the GP program

Table 2 | Participant demographics.

Location	Sex	Age	Length of stay (months)	Follow-up
Arbutus Care Centre	M	63	11	Yes
	M	90	23	Yes
	F	90	20	Yes
	F	95	11	Yes
Point Grey Private Hospital	M	87	9	Yes
	F	80	19	Yes
	F	83	9	No – moved away
	F	90	12	No – passed away
Average age		85		
Average Length of Stay			14	

strengthened these participants' pre–existing motivations (Table 3).

Activities

All participants reported enjoying GP, citing reasons including a refreshing change in environment, improved mood, opportunity for interpersonal interactions, and opportunity to be engaged in an activity (Table 4). At the end of the program, no participants reported any change to the number or variety of activities they were involved in. All participants indicated that they would like to continue with the program in the future, although two expressed some reservations due to their old age.

Relationships

Participants emphasized that their most important relationships were with their family and long–time friends regardless of frequency of contact (Table 5). All participants found it difficult to build friendships within the care facilities, citing reasons like communication difficulties and lack of trust. None of the participants felt a sense of closeness with the staff; in general, they maintained an amicable working relationship. Involvement in GP generally did not impact the participants' relationships with family, fellow residents or staff. One participant noticed a significant improvement in interpersonal relationships; a social program like GP helped the participant become more outgoing (Table 6).

Autonomy

Participants defined autonomy as the freedom to make their own decisions and do the things they want. At the pre–program interviews, four out of eight participants felt autonomous, while others felt restricted by the care facility environment or by old age (Table 7). Participants reported no change in their self–perceived level of autonomy at the end of the program..

Discussion

Theme 1: GP strengthened the participants' pre–existing motivations

Guse and Masesar found that QoL was significantly improved when residents of a care facility felt that they were able to help others.[8] Thus, GP was framed as an opportunity for the senior participants to teach young children about life, aging, and residential care. It was thought that this would positively affect the seniors' global motivations domain and drive them to develop new healthy behaviours. However, we did not find this to be a major theme. Instead, we found that most seniors did not make any changes to their daily routines; only those who were already motivated to engage in healthy behaviours, such as interacting with others and performing rehabilitation exercises, felt more compelled to do so after participating in GP. It seems that the program did not create motivations towards one's health but did strengthen the participants' pre–existing motivations. While participant 3 increased his/her exercising after partaking in GP, he/she had always strived to be active to prevent becoming "a slob of a person". Our findings correlate with literature on motivation in institutionalized seniors, which found that personality is the major determinant of motivation,[9] making it difficult to change. Of note, a third of our participants stated that they felt too old for any lifestyle changes.

New motivations may be encouraged by helping seniors set meaningful and achievable goals.[9] Continuous active support by primary caregivers is also a major catalyst in increasing motivations.[10] In the future, participants of GP can partake in a goal–setting session with primary caretakers prior to starting the program. Throughout the program, primary caretakers and program leaders can utilize motivational techniques such as verbal cues and encouragement, role modelling and humour to help participants achieve their goals.[10] Potential barriers include participants' physical limitations, increased utilization of health care resources and staff training.

Table 3 | Comparison of participants' pre- and post-program motivations.

Pre-program opinions	Post-program opinions
"I have lots of friends, sometimes I join the community centre, do this and do that, and see a lot of friends." (P2)	*"After playing with the kids, I am more motivated to build relationships and value life more." (P2)*
"If I don't do it, I'm surely going to be a slob of a person." (P3)	*"Another activity that I have started to do myself is to get out of this chair, hold onto the handles and start walking because MS doesn't get better by itself, and you have got to keep the muscles working. You want to look good, not like a years old gran." (P3)*

Table 4 | Advantages and benefits of the Grandpal Penpals program identified by participants.

Theme identified (number of responses/total participants)	Participant opinions
Change in environment (3/6)	*"I liked going to the school. They have a lot more things going on at the school than we have for them here. I'd like to go back again." (P4)*
Improved mood (4/6)	*"Helped me with my mood. I read the letters, and it kind of boosted me up a little bit in the morning." (P4)* *"Oh I loved the visits. [The kids] all come running to you. That's the nicest feeling." (P6)*
Interpersonal interactions (5/6)	*"I enjoy social programs like Grandpal Penpals as I can converse and share thoughts with others. I feel happy seeing the students because they remind me of my past relationships with my kids." (P2)* *"I really enjoyed it, we really do correspond." (P3)*
Active Engagement (6/6)	*"At the care home, there are not many fun activities so seeing the students was quite refreshing." (P2)* *"If there are any activities I would be fascinated to learn about here. I don't know any activities going on." (P3)* *"It's got a real benefit. There's nothing here to do! That was great, one of the best things they've done." (P6)*

Theme 2: Seniors perceived social programs like GP to be enjoyable and beneficial while actively involved

All of the participants reported that life in residential care facilities was too monotonous, with too much spare time and too little stimulation. This finding is in line with the results of another study which showed that institutionalized seniors spend 65% of their time doing little or nothing, and only 12% of their time in social activities even in a facility with a high standard of care and a creative activities department.[11] GP was considered a refreshing change in environment that provided an opportunity for interpersonal interactions and additional activities. Most participants experienced markedly improved mood during letter writing and visits, and some improvement when they revisited the letters in between program activities.

To potentiate the benefits of the program, GP could increase the frequency of letter writing and visits. More visits could be held outside of the residential facilities, such as at schools and other public spaces. Older students may be able to accompany seniors to a greater variety of physically and mentally stimulating activities. These changes to GP

could further help break up the monotony that institutionalized seniors experience.

We hoped that a positive experience with GP would activate the seniors to seek out other rewarding activities; however, the seniors reported no change in the number or variety of activities. This is unlikely due to a lack of motivation as most seniors reported a desire to be involved in similar social programs. Half of the senior participants indicated that they were either unaware of or not interested in the activities offered by the care centre. More investigation is required to determine barriers seniors may face to participating in recreational activities, including whether care facilities are offering sufficiently diverse activities and properly advertising them to all residents.

Theme 3: Most participants found that GP did not affect their interpersonal relationships

A study by Moon found that long–term friend and family relationships greatly influenced QoL.[12] Similarly, the senior participants unanimously valued family and long–term relationships above all others, regardless of the frequency of contact. Previously, O'Connor found that the quality of relationships was a stronger predictor of life satisfaction in seniors than frequency of contact.[13] Considering that institutionalized seniors tend to form superficial relationships with fellow residents and staff,[14] it is understandable that they would place greater value on deep relationships with family members even if they scarcely visit. Furthermore, the senior participants often found it difficult to meet like–minded individuals in residential care. Higher functioning participants revealed it was difficult to converse with residents suffering from significant cognitive and physical decline. Previous studies support these sentiments; a common theme in peer interaction within care facilities is to stay away from individuals who cannot reciprocate.[15,16] Studies have found that residents tend to have superficial interactions with peers and staff; rarely do seniors discuss personal topics with them.[14] Despite this, encouraging interactions with fellow residents is important; in fact, one study suggested that participation in social activities outside the family may have a bigger positive impact on cognitive function than social contact with family members.[17]

All but one of the senior participants reported that they noticed no change in their relationships with family, fellow residents, and staff. One participant specifically indicated that he/she kept family relationships very private and separate from GP. Another participant was resigned to the idea that his/her relationships could not be changed. Only one participant indicated that the program helped him/her to become more outgoing, which benefitted all of his/her relationships. It appears that although GP could help develop social skills in those who are more shy, seniors face other barriers to making and maintaining relationships that were not addressed by GP.

Moving forward, potential improvements to GP include active facilitation of resident–resident interaction by care staff. For example, staff can help residents write letters in groups of two, which would allow the residents to converse about each other's pen pals. Setting more personal themes for the letters can encourage the residents to have deeper conversations with the students and with each other. The social visits can incorporate more activities that involve resident collaboration, as opposed to separating residents into their pen pal groups. Higher–functioning residents can even help to design and lead activities. To facilitate and preserve important connections with

Table 5 | Participants' opinions of their relationships with family, other care facility residents and staff.

Relationships	Participant opinions
Family	*"Just my family, really, they're the most meaningful." (P1)* *"I can hardly remember the last time I saw [my family]. I saw them a few times earlier in the year. My relationships with them are still very good though." (P5)* *"I have a son and 4 grandsons. I don't see them often because they all have busy schedules. I don't feel rejected by it because I understand what it is like to be busy." (P3)* *"I still have close relationships with them. When I fell and I was bound to a wheelchair, they still came to visit often, especially my eldest daughter." (P7)* *"Two or three old-aged ladies, we can meet together every one or two weeks." (P2)*
Other Residents	*"The people here are not mentally sound. I find it hard to make friendships. Some people here are hardly human beings." (P3)* *"The sociability here is not the same as the place I used to live in. We had a bridge game every afternoon, and you made friends with people. And here you don't seem to. The only people that I really talk to are three times a day at the meal." (P3)* *"Communicating with others and keeping their attention is a hard part." (P7)* *v* *"Well, most of them are asleep. So you can't make relationships with someone who's asleep." (P4)* *"They are alright. But I can't really confide in them. And some of the residents can't keep anything without telling somebody. So many of them are like that. So you have to be careful about what you tell them." (P6)* *"My associates, they are not close friends." (P5)* *"I wouldn't interact with them. I just wouldn't want to with them." (P1)*
Staff	*"I am not close with any of them. But most of them are quite nice, and they take care of things pretty well." (P5)*

Table 6 | Impact of the Grandpal Penpals program on interpersonal relationships.

Impact	Participant opinions
Improvement	*"It opened the doors for me. I'm not as shy as I was." (P6)*
No change	*"No, not really…You get used to the people around you." (P1)* *"Not really. It is a private relationship, and I certainly don't talk to them, especially the younger kids about [my family]." (P3)* *"It doesn't have any impact [on how I interact with others at the care home]." (P4)* *"I don't think there are any changes." (P5)*

Table 7 | Participants' pre-program opinions on their level of autonomy.

Level of autonomy	Participant opinions
Autonomous	*"I would say I have had control over my decisions for quite a while." (P7)* *"I can still go places that I like to go. I'm very happy with this." (P2)*
Non-autonomous	*"You have to sign a book at the desk... every time you go out. I don't want to do that." (P4)* *"Decisions in my life are coming to an end. I eat three meals a day. And I am allowed to read until 1 o'clock in the morning if I want to." (P3)*

family, one session of GP can focus on promoting technology use to seniors, such as video chat. Student participants are typically skilled with iPads and computers, and can teach their senior pen pals how to use these tools to communicate with family and friends. Potential barriers to promoting technology include cognitive limitations of some seniors, equipment access, and funding. The seniors may have a greater opportunity to develop meaningful relationships with the students if the program was extended over a few years with the same children. However, this is logistically difficult as students move to different classes each year.

Theme 4: GP had no impact on the participants' self–perceived level of autonomy

Many participants recognized the need for a residential care facility and had learned to live within their physical, cognitive, and environmental limits; these individuals did not perceive any loss of autonomy. This is contrary to existing literature which suggests that self–perceived autonomy increases with increased functional ability.[18] On the other hand, those who were adamant about independent living strongly despised the limitations that care facilities imposed on them; they felt that the rules made daily activities much more difficult. This is supported by a 2004 study that showed the nursing home environment required residents to overcome greater challenges to maintain their autonomy and activities of daily living than would have been expected at home.[19]

GP has little role in changing the rules of the care facilities; however, the program does expand the limits of what the seniors are allowed to do, such as leaving the care facilities for school visits. Participants expressed that more participation in the program may help improve their autonomy. Therefore, implementing more visits and increasing the duration of the program may potentiate its effects.

Research limitations

Although we designed the interview questions to be concise and direct, they were often still too abstract for our research participants to fully understand. In addition, the differences in rapport with different interviewers may affect participants' responses even though efforts were made to standardize the interviews.

Although we had excluded seniors with severe dementia who were incapable of providing informed consent, interviewing seniors with mild neurocognitive disorders was still a significant difficulty. Some participants had trouble sustaining attention through a 30–minute interview and occasionally found it difficult to associate GP with our interview questions. Researchers used frequent redirection and clarification to address this issue. It might appear simpler to exclude this population altogether, but as they make up a great percentage of seniors living in care facilities, inclusion is more reasonable for proper representation of our study population.

Differences between the two residential facilities might have impacted the participants' experiences. For example, the activity space in Arbutus Care Centre was much smaller than that in Point Grey Private Hospital, which led to a more crowded and noisy environment that participants may have found distracting. Also, participants at Point Grey Private Hospital did not have the transportation services to visit their pen pals at the elementary school, and thus did not experience a change in environment that other seniors found enjoyable.

We did not collect information on other factors that may have affected participants' experiences with GP, such as cultural background, language preference, medical conditions, experience with children, and personality.

Although invaluable detailed information has been collected from each participant, it is difficult to generalize the findings to a larger population with a small sample size of eight.

Conclusion

Our team conducted qualitative research to evaluate seniors' QoL in residential care facilities and how it may be affected by an intergenerational social activity like GP. Major themes were identified in the domains of motivation, activities, relationships, and autonomy: 1) GP strengthened the participants' pre–existing motivations, 2) participants perceived social programs like GP to be enjoyable and beneficial while actively involved, 3) most participants found that GP did not affect their interpersonal relationships, and 4) Grandpal Penpals did not affect the participants' self–perceived level of autonomy. In the future, we hope to investigate whether highly engaging, long–term social programs with increased senior–senior or senior–family interaction and individualized goal setting would be of greater benefit.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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Incidental hyperkalemia: An unusual and unexpected case of severe hyperkalemia in an otherwise stable post–liver transplant recipient

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Abstract

Hyperkalemia is a potentially life–threatening electrolyte abnormality. We describe a case of severe hyperkalemia secondary to the combination of immunosuppressant, antibiotic, and antifungal therapy in a liver transplant patient. A 68–year–old man in stable condition was found to have a serum potassium level of 7.9 mmol/L one year after an orthotopic liver transplant. Other causes of hyperkalemia were ruled out and his hyperkalemia resolved with conventional therapy and adjustment of his medications. With an increasing number of post–liver transplant patients in British Columbia, similar clinical situations may become more frequent. This case illustrates the importance of regular monitoring of this patient population.

Background

The concentration gradient of potassium across cellular membranes is crucial in the regulation of the resting membrane potential of excitable cells. Deviations from the normal range can result in significant cardiac, neuromuscular, and metabolic manifestations. Hyperkalemia, generally defined as serum concentration of potassium greater than 5.0mmol/L, is a common clinical issue.[1] The potential causes of hyperkalemia are numerous, but can be broadly grouped into the following categories: increased exogenous intake, increased cellular release, and reduced urinary excretion; medications can contribute to the latter two.[1-2] Here we present a case of hyperkalemia in a stable post–liver transplant recipient taking a combination of medications that contributed to decreased potassium excretion.

Case

A 68–year–old male of Indo–Canadian background presented to the emergency department after a routine laboratory test reported a serum potassium level of 7.9mmol/L.

Eleven months earlier, he had received an orthotopic liver transplant for decompensated liver cirrhosis secondary to primary sclerosing cholangitis. Prior to his transplant, a computed tomography scan of his abdomen incidentally showed a 3cm opacity in the left lower lobe of the lung. Analysis of bronchoalveolar lavage confirmed cryptococcal infection. After consultation with the infectious diseases service, the patient was started on high–dose fluconazole therapy at 400mg daily, which was to be continued for one–year post transplant. About nine months after his transplant, the patient developed bilateral shoulder pain and swelling in the extremities. He was seen by the rheumatology service, and a 10mg daily dose of prednisone was started for preliminarily diagnosed psoriatic arthropathy. Other medications taken by the patient included tacrolimus 1.5mg twice daily (BID) and mycophenolate mofetil 500mg BID for maintenance immunosuppression. The patient was taking trimethoprim/sulfamethoxazol (TMP-SMX) 160/800mg three times per week for *Pneumocystis carinii* pneumonia prophylaxis post–transplant, but this had been discontinued a few weeks prior to presentation.

His past medical history also included long–standing ulcerative colitis, for which he took mesalamine, variceal bleeding due to portal hypertension, proton pump inhibitor therapy, and benign prostatic hypertrophy, for which he underwent a transurethral resection of prostate procedure three months post–transplant.

Post–transplantation, the patient underwent regular outpatient blood tests for monitoring of medication levels and attended regular appointments with both the solid organ transplant and the infectious disease services. Of note, there had been a history of mild intermittent hyperkalemia, not exceeding 6.0mmol/L, last documented nine months prior to presentation.

When the patient arrived at the emergency department, he was experiencing no symptoms of hyperkalemia, such as chest pain, palpitations, nausea, parasthesias, or fatigue.[1] His physical examination was unremarkable and an urgent ECG did not show features consistent with hyperkalemia, such as flattened P waves, QRS widening, peaked T waves, or conduction blocks.[1] Admission bloodwork was also significant for an increase of creatinine level of 126μmol/L (eGFR 50mL/min) from the patient's baseline of around 80-100μmol/L. Arterial blood gas showed pH of 7.36, close to the lower limit of normal, pCO2 of 33mmHg, and HCO3- of 18mmol/L. His complete blood count was unremarkable, liver function tests were normal, and tacrolimus level was at 6.5μg/L (therapeutic range 4.0-8.0μg/L). Urine electrolyte values were collected around five hours after admission and initial management and therefore were omitted here.

The patient was promptly given calcium gluconate for cardiac protection. Insulin was given with complimentary 50% dextrose to shift potassium into intracellular space. Sodium polystyrene sulfonate (Kayexalate) was given for binding of intestinal potassium. In addition, normal saline was given intravenously to correct his acute kidney injury. Repeat bloodwork showed return of potassium and creatinine to normal levels within the next 24 hours. He remained normokalemic overnight and his creatinine level normalized to around 100μmol/L.

The patient was discharged from hospital in stable condition. Since tacrolimus is associated with hyperkalemia (see discussion), the dosage was adjusted from 1.5mg to 0.5mg BID upon discharge. One week after discharge, outpatient bloodwork showed a mild increase in potassium levels once again, to 5.0mmol/L, requiring him

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to take a five–day dose of Kayexalate which returned his potassium to 4.0mmol/L. Once off Kayexalate, the patient's potassium levels returned to 5.3mmol/L. In consultation with the infectious diseases team, it was thought that fluconazole, perhaps in combination of his other immunosuppressive drugs, continued to contribute to hypoaldosteronism and decreased potassium excretion. Therefore, his fluconazole was stopped. Hyperkalemia has not recurred in this patient after this episode.

Discussion

Hyperkalemia is known to be associated with increased mortality and morbidity.[3] One nonfatal case of a potassium level of 14mmol/L has been previously reported, but it is generally accepted that serum levels greater than 6.0mmol/L require immediate management, especially if the rise in potassium occurred acutely.[1,4] Many factors can contribute to hyperkalemia. In this case, hyperkalemia was caused by reduced renal excretion associated with polypharmacy and a decline in GFR.

Decreased GFR of any cause, including acute or chronic renal failure or low effective circulating volume, leads to decreased sodium delivery to the distal nephron.[1,5] A decrease in sodium reabsorption by the selective epithelial sodium channels (ENaC) located on the apical surface of principle cells leads to a less favorable electrical gradient for the excretion of potassium into the lumen through the renal outer medullary potassium (ROMK) channels, also located on the apical surface.(Table 1).[2] Hypoaldosteronism of any cause also leads to decreased renal excretion of potassium, as the number of open ENaCs and the function of Na-K-ATPases are under the control of aldosterone.[1,2] Hypoaldosteronism can result from adrenal insufficiency, as in Addison's disease or from decreased production of aldosterone as a result of medications such as angiotensin-converting enzyme inhibitors (ACEi).[5] Alternatively, patients can be in a hyporeninemic hypoaldosterone state, such as type IV renal tubular acidosis.[1] Medications may also induce aldosterone resistance in the distal nephron.[5] Medications known to cause this side effect include potassium–sparing diuretics such as spironolactone, calcineurin inhibitors such as tacrolimus or cyclosporine, and antibiotics including TMP, among others.[5] Finally, dysfunction in the sites of renal potassium excretion, as seen in the various types of renal tubular acidosis, are known to present with metabolic acidosis and hyperkalemia.[2]

The patient in the present case had several risk factors for developing hyperkalemia. His GFR was low on presentation for unclear reasons. A reduction in extracellular fluid volume is a very common reason for a low GFR and reduces sodium delivery to the distal tubule, which in turn, limits potassium excretion. This effect may explain the reduction in the patient's potassium level after normal saline was given. Tacrolimus has been known to cause decreased GFR.[8] The mechanism behind this relationship has been postulated to be multifaceted, including direct injury to the endothelium and decreased production of prostaglandins and other vasodilators.[8-9] In addition, tacrolimus has also been shown to inhibit Na-K-ATPase, leading to decreased transepithelial potassium secretion, as well as cause renal tubular acidosis in the distal tubules.[8-9] Despite these known adverse effects, immunosuppression–induced hyperkalemia and acid–base imbalance is uncommon after liver transplant.[8] Indeed, only three such cases have been reported so far.[8,10-11] Another significant contributor to hyperkalemia in this case is likely the long–term use of TMP–SMX, even though it was discontinued just before presentation. TMP blocks the ENaCs much like potassium–sparing diuretics, effectively causing functional hypoaldosteronism.[1,12] TMP–SMX in standard dosage is fairly well tolerated, especially given the relatively short half–life (6-12 hours).[13] However, its use in patients with kidney injuries or who are taking medications including NSAIDs, ACE inhibitors, and calcineurin inhibitors warrants regular monitoring.[14] Fluconazole has also been reported to be associated with severe hyperkalemia in the pediatric population as well as reported to be associated with functional adrenal insufficiency, including mineralocorticoid insufficiency.[6-7] It is of note that active fungal infections are a contraindication to liver transplantation. However, in this patient's case, the cryptococcal lung infection pre–transplant was adequately treated and he was in the maintenance phase of treatment and monitored by the Infectious Diseases service.

Table 1 | Sites of Potassium Handling and Drug Activity in the Kidney
Sites of potassium handling and activity of drugs relevant to this case. K: Potassium; TAL: Thick Ascending Loop; DL: Distal Tubule; CCD: Cortical Collecting Duct; TMP-SMX: Trimethoprim/Sulfamethoxazol; SE: Side effect

Site	K Movement	Active drugs
TAL	Reabsorption	Loop Diuretics
DT	Excretion	Thiazide Diuretics
CCD (Principle Cells)	Excretion	K Sparing Diuretics TMP-SMX (SE)

In summary, this asymptomatic post–transplant patient presented with potentially life–threatening hyperkalemia. The cause was most likely multifactorial, including medications specific to the transplant process. With a growing population of post–liver transplant patients in B.C., it can be expected that this patient's clinical situation will be encountered again in the future.

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Case report: Ileocecal tuberculosis

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Abstract

Tuberculosis (TB) can affect any organ system and resemble multiple disease entities, thus it is often called the "great mimicker". We discuss the imaging features and challenges of diagnosing extrapulmonary TB—specifically gastrointestinal manifestations of TB—in our case of a 25 year–old immigrant from Southeast Asia. The diversity of manifestations of TB should alert the reader to keep this elusive disease on their differential diagnosis.

Introduction

Tuberculosis (TB) is frequently thought of as a disease of the developing world, however incidence in Canada is not uncommon, with about 26 and 17 cases per 100,000 persons/year among Aboriginal and foreign–born Canadians respectively, with even higher rates among immunocompromised individuals.[1] While often limited to the pulmonary system, TB may affect the bones, joints, heart, central nervous system, and abdomen—a region involved in up to 11 % of extrapulmonary cases of TB.[2] A brief list of the abdominal manifestations of TB includes: TB lymphadenitis, peritonitis, gastroenteritis, as well as possible masses within and enlargement of the spleen, liver, adrenals, and pancreas.[2] The signs and symptoms of TB are usually generalized and nonspecific, with imaging features frequently resembling other disease entities, giving TB the pseudonym "the great mimicker."[3] The challenging diagnosis of extrapulmonary TB is usually made by the combination of imaging and microscopy. Histopathologic analysis uses a special technique called a Ziehl–Neelsen, or acid–fast bacillus (AFB) stain, as the *Mycobacterium tuberculosis* bacteria are impermeable to Gram staining due to their waxy outer layer.

To highlight the challenges of diagnosing extrapulmonary TB, we discuss a curious case of pulmonary TB which was also found to involve the gastrointestinal system.

Case presentation and workup

A 25–year–old female recent immigrant from Southeast Asia is admitted to hospital for abdominal pain and fever not yet determined. Her history of presenting illness includes a two–year history of productive cough, significantly worsening over the last one month and associated with fevers and chills. She endorses shortness of breath but denies hemoptysis. Other infectious symptoms include worsening diarrhea over the past five days with some bright red blood per rectum.

Her past medical history is unremarkable aside from an appendectomy. Her only risk factors for infectious etiology include travel to China six months prior. She has not traveled to rural areas or had exposure to sick contacts. She is a non–smoker, non–drinker, and is not sexually active. Her review of systems is negative for any rheumatologic or constitutional symptoms.

Her vital signs include a fever of 39.5 ºC, tachycardia, and tachypnea. Her blood pressure is normal and she is saturating well on two liters of supplemental oxygen via nasal prongs. Respiratory exam reveals bronchial breath sounds and decreased air entry to the right lung base. Other components of her physical exam are unremarkable.

Initial laboratory workup shows a white blood cell count of $13.8x10^9$/L and a microcytic anemia with hemoglobin of 88 g/L Her renal function and urinalysis are normal. In regards to her yet to be determined fever, she was started on piperacillin–tazobactam and was sent for a chest x–ray. Her x–ray revealed bilateral nodular opacities and lymphadenopathy (Figure 1). A broad differential for diffuse pulmonary nodules on chest x–ray includes sarcoidosis, granulomatosis polyangitis, septic emboli, as well as tuberculosis. The combination of signs, symptoms, physical exam, and chest x–ray findings in a foreign visitor put this patient at a high pre–test probability of having TB.[4] Our patient was placed in isolation, during which time her sputum sample came back as positive for acid–fast bacteria. The piperacillin–tazobactam was discontinued and she was started on standard quadruple TB therapy: rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1250 mg, and ethambutol 800 mg.

She continued to have persistent fevers and began to complain of worsening diarrhea and rectal bleeding, the clinical differential of which includes inflammatory bowel disease, diverticulitis, ischemic bowel, or infectious causes such as *cytomegalovirus (CMV)* or abdominal manifestation of TB. The six–month lag symptom onset and her travel to China made an acute travel related infection unlikely. Her differential diagnosis was further narrowed by a negative stool culture, ova and parasite examination, and *Clostridium difficile* test. She did not have an elevated lactate and her serology was negative for CMV, Hepatitis, and HIV.

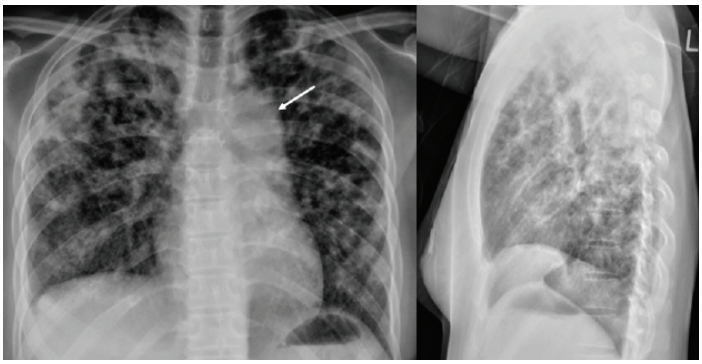

Figure 1 | Postero–anterior and lateral chest radiographs. Numerous and diffuse bilateral soft tissue densities are seen with no evidence of cavitation, in addition to a small right sided pleural effusion. Mild mediastinal lymphadenopathy is indicated by loss of normal aortopulmonary window (white arrow).

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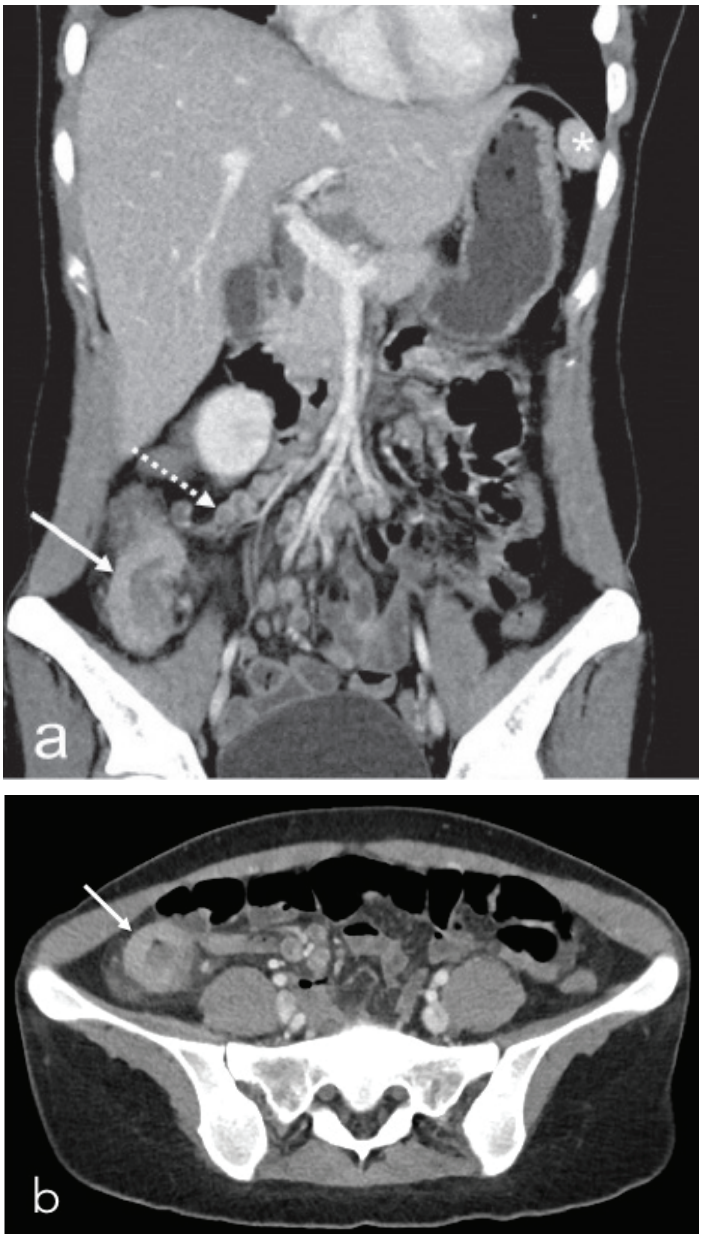

Figure 2 | (a) Coronal and (b) axial contrast enhanced CT abdomen and pelvis. Marked focal mural thickening and enhancement of the right hemicolon and terminal ilieum (white arrow), with multiple small necrotic nodes in the ileocolic fat. Extensive mesenteric lymphadenopathy with nodes measuring up to 1 cm in diameter with central areas of necrosis (dashed arrow). Other than a small accessory spleen (*), there are no focal abnormalities.

An abdominal computed–tomography (CT) scan was requested, which revealed significant ileocecal mural thickening and necrotic lymphadenopathy (Figure 2). The presence of ileocecal thickening on imaging can be present with Crohn's disease (CD), malignancy, or TB, and although necrotic lymphadenopathy can also be seen in malignancy and TB, it is not usually present in inflammatory bowel disease.

Combining her clinical and imaging findings, the working diagnosis was Crohn's disease or extrapulmonary manifestation of TB—specifically ileocecal TB (ITB). Using the simplified algorithm in Figure 4, one can see that both CD and ITB are grouped together under granulomatous diseases, thus one cannot differentiate CD from ITB based on bowel wall thickening pattern alone. In addition,

Table 1 | Commonly found features of Crohn's disease and ileocecal tuberculosis on abdominal computed–tomography scan. Fistulas and abscesses are italicized as they are contested to have a similar occurrence in both. Derived from Journal of Digestive Diseases 2016; 17; 155-161.[6]

Crohn's Disease	Intestinal Tuberculosis
Segmental Involvement	Focal involvement
Asymmetric mural pattern	Right colic artery predilection of lymph-adenopathy
Mural stratification	Lymph nodes ≥ 1 cm
Left colon involvement	Central necrosis/calcification of lymph nodes
Comb sign (vascular congestion of vasa recta)	Fistulas and abscesses
Fibrofatty proliferation	
Fistulas and abscesses	

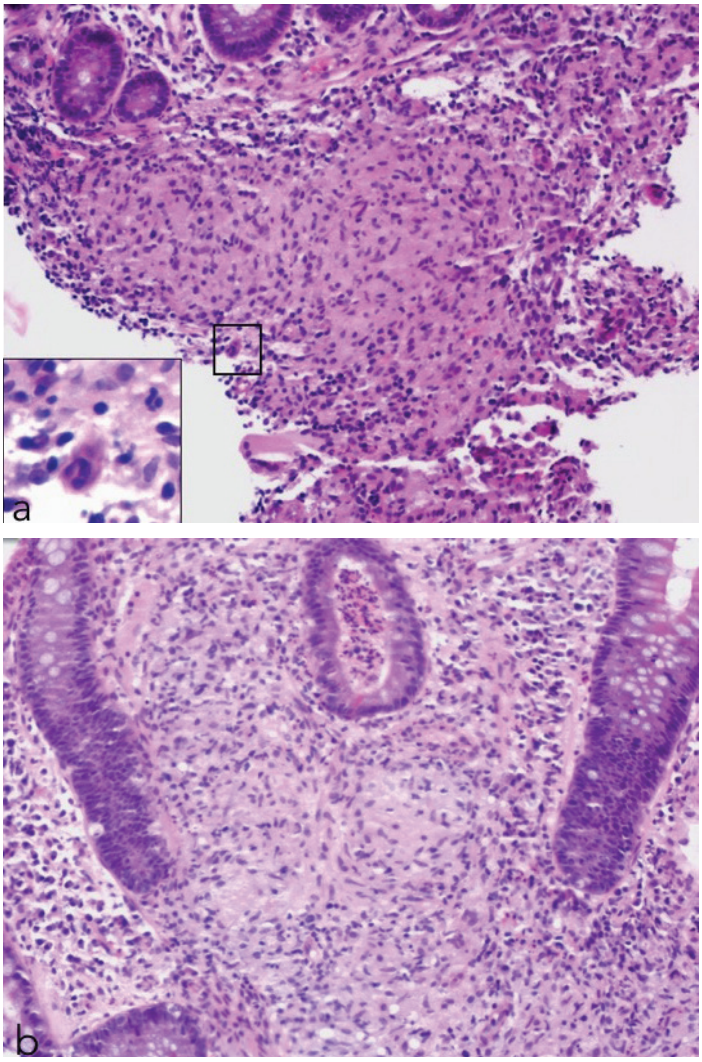

Figure 3 | Hematoxylin and eosin stain of colonic biopsy at (a) low and (b) medium power show multiple concentrations of granulomatous inflammation with central areas of necrosis. A Langhans type giant cell is magnified on the inset of (a).

the absence of intestinal strictures, fistulas, or abscesses associated with Crohn's, or any extraintestinal manifestations such as cirrhosis, cholelithiasis, and nephrolithiasis is neither a sensitive nor specific finding to narrow the diagnosis.

Kedia et al. attempted to develop criteria differentiating CD from TB and showed that lymph nodes greater than 1 cm and ileocecal involvement had odds ratios favouring ITB, however due to multiple outliers and exceptions, there are ultimately no exclusive imaging predictors.[5] A 2016 review of ITB and CD describes

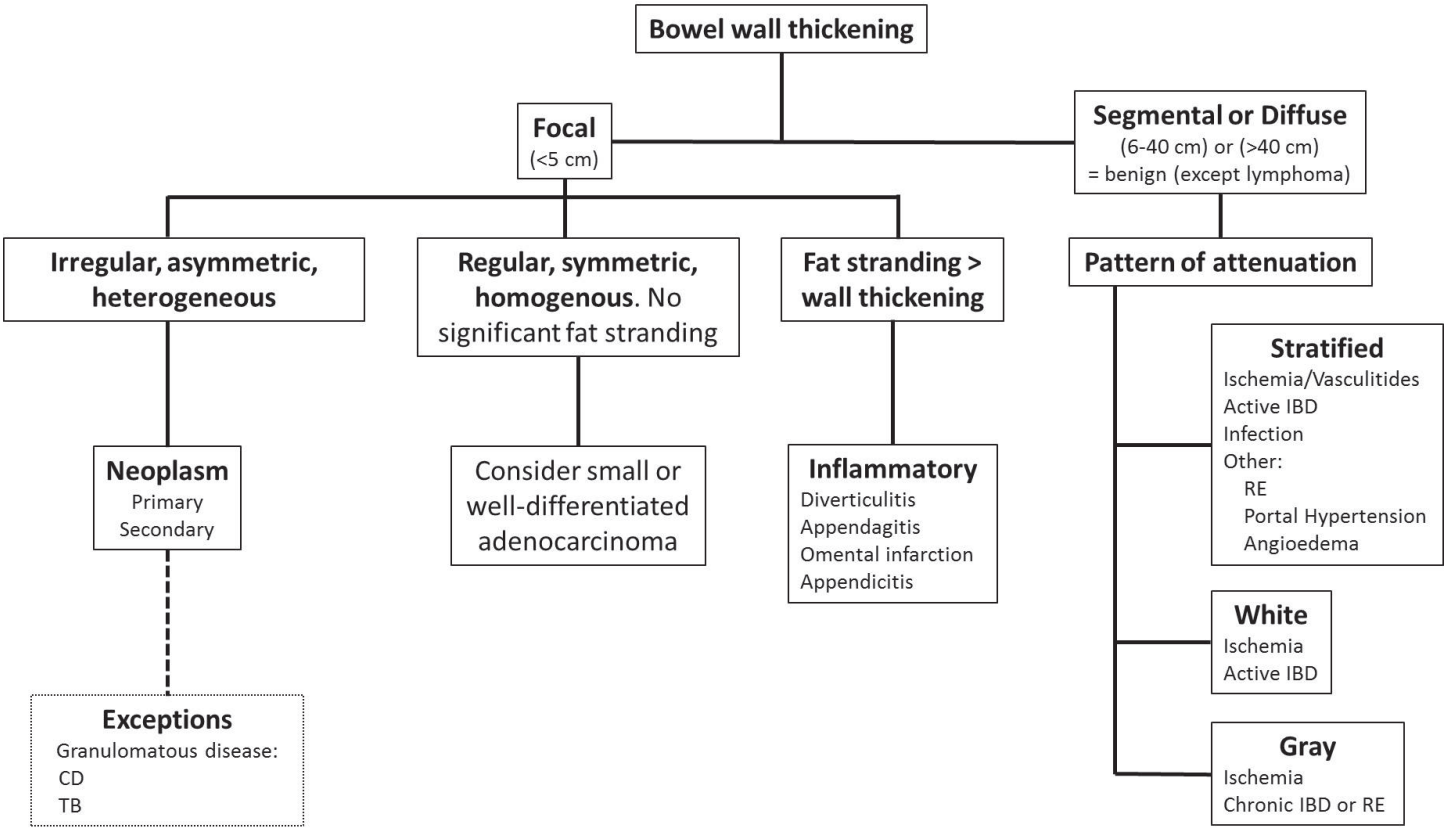

Figure 4 | Simplified algorithmic approach to bowel wall thickening. IBD; inflammatory bowel disease. RE; radiation enteritis. CD; Crohn's disease. TB; tuberculosis. Modified from Insights Imaging (2014) 5:195-208.[8]

imaging characteristics more commonly found in one disease process versus another (Table 1), but confirms the lack of specific criteria to reliably differentiate the two.[6]

Case conclusion

To arrive at a definitive diagnosis, the patient underwent a colonoscopy and ileocecal biopsy. Microscopy exhibited extensive areas of granulomatous inflammation (Figure 3). Granulomatous inflammation in itself is a nonspecific finding, as it can be observed in a multitude of fungal, bacterial, and viral infections in addition to Crohn's disease, sarcoidosis, and granulomatous polyangitis. However, given the presence of Langhans type giant cell, characteristically found in TB granulomatous inflammation, and the lack of crypt abscess or mucosal ulceration to suggest Crohn's disease, her diagnosis was most in keeping with *TB enteritis*. Although an AFB stain of the biopsy was negative – not uncommon after initiation of *TB antibacterials* – the sample was subsequently found to be culture positive for *M. tuberculosis*.

The case was confirmed to be dissemination and extrapulmonary manifestation of TB within the gastrointestinal tract. The treatment for abdominal TB is the same as for active pulmonary TB, thus the patient was kept in isolation and received daily quadruple therapy. Due to persistent fevers and continued positive sputum cultures, the dose of her rifampin, isoniazid, and ethambutol were increased to 900 mg, 600 mg, and 1200 mg respectively. She underwent two months of in–hospital therapy under this regime, and at six weeks was deemed non–infectious as a result of negative sputum cultures. She was discharged on a six–month course of daily isoniazid 600 mg, rifampin 900 mg, ethambutol 1200 mg, and pyridoxine 50 mg.

Discussion

Our patient presented with features quite typical for an active pulmonary TB infection. She was a visitor from an area with a high endemic rate of TB and endorsed a history of chronic productive cough associated with dyspnea, fevers, chills, and general malaise. A positive sputum AFB stain combined with evidence of pulmonary involvement on chest x–ray confirmed an active infection and warranted isolation and initiation of quadruple TB therapy. Our initial workup of her gastrointestinal symptoms (as described above) narrowed our differential diagnosis to that of inflammatory bowel disease or intestinal manifestation of TB—entities which can be so similar they received special attention in a 2016 review "Intestinal tuberculosis and Crohn's disease: challenging differential diagnosis."[6]

Our case was made especially challenging given that our patient already had an active pulmonary TB infection. While an active TB infection increases the likelihood that abdominal symptoms are related to ITB, the presence of mycobacterium in patients with CD is theorized to act as an inflammatory nidus triggering a CD flare.[6] Furthermore, positive sputum cultures or serologic tests for TB, such as an interferon gamma assay that measures cytokine release from immune cells exposed to *M. tuberculosis* antigen, would not help distinguish ITB from CD in our patient. Even stool analysis with polymerase chain reaction (PCR) for *M. tuberculosis* DNA—considered more specific for ITB—could yield false positive results given the possibility of patients with active pulmonary TB swallowing infected sputum. Serologic tests for CD, such as anti-*Saccharomyces cerevisiae* antibody (ASCA) test, could help in the diagnosis of CD and even differentiate CD from ulcerative colitis, however similar positive rates occur in patients with ITB as in CD,

limiting its usefulness in our setting.[6]

Another diagnostic tool that could be used includes aspiration and analysis of ascitic fluid in patients with suspected gastrointestinal TB. Findings suggestive of TB in peritoneal fluid include an exudate with > 300 white blood cells/mm3, a serum–ascites albumin gradient < 1.1 g/dl, or a positive adenosine deaminase assay (ADA).[7] Unfortunately, our patient did not have a clinically significant level of peritoneal fluid for safe paracentesis.

As discussed in our case presentation, cross–sectional imaging alone cannot accurately differentiate ITB from CD. Histopathalogic analysis is required for confirmation of ITB with the gold standard being the presence of caseous granulomas and a positive AFB. Here again, our diagnosis was made more challenging secondary to initiation of antibiotic therapy for active pulmonary TB producing a negative AFB stain of our patients' ileal biopsy. A confirmatory diagnosis for ileocecal TB was only possible after several weeks when her specimen was found to be mycobacterium culture positive.

The diagnostic challenges presented herein can be quite common, with a misdiagnosis between ITB and CD quoted to be between 50-70 %.[6] And although treatment for CD and ITB differ, the treatment of extrapulmonary TB is the same as for pulmonary TB (daily quadruple drug regime). Because our patient was already started on TB antibiotics, she was concomitantly receiving appropriate empiric therapy for her abdominal symptoms even amidst her diagnostic dilemma. Current literature recommends that when considering CD versus ITB, and where ITB is highly suspicious, that anti–TB chemotherapy be initiated with a therapeutic trial of two to three months and monitoring for clinical improvement.[6]

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Acute flare of ulcerative colitis resulting in perforation and managed with colectomy: Case report and literature review

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Abstract

We present the case of a 34 year–old male with a previous diagnosis of ulcerative colitis, who presented with an acute flare resulting in bowel perforation and pneumo–peritoneum ultimately requiring total colectomy. Acute presentation of ulcerative colitis is a potentially life–threatening medical emergency requiring immediate medical treatment to induce disease remission and address any superimposed infections. Complications of acute ulcerative colitis include bowel perforation and toxic megacolon, particularly after colonoscopy. Extra precautions should be taken when planning colonoscopy for these patients to reduce the risk of such perforation. We outline the diagnosis, management, and complications associated with acute flares of colitis.

Patient History

A 34 year–old male with a history of pan–ulcerative colitis presented to the hospital after 10 weeks of diffuse abdominal pain, fevers, chills, nausea, emesis, and approximately 20 loose, bright red, bloody, bowel movements per day. His ulcerative colitis was diagnosed in 2012 and at the time of admission was managed with infliximab (Remicade) every six weeks and daily prednisone. He reported one prior flare of colitis a year ago, which was treated medically. At admission, his vitals were stable and he was afebrile. His abdomen was mildly diffuse and tender. There were no signs of peritonitis.

At admission, a sigmoidoscopy was performed reaching 35 cm from the anal verge. The mucosa was very friable and deep ulcerations were present, indicating a Mayo Grade of 3 (Mayo Grade indicates severity of ulcerative colitis from 0 to 3, based on endoscopic findings). An abdominal X–Ray at that time demonstrated features of colitis with a maximal diameter of 7.2 cm noted at the transverse colon. The patient's C–reactive protein (CRP) was 362 mg/L at this time. He was subsequently started on IV methylprednisolone and IV ganciclovir (Cytovene), as there was initial concern of cytomegalovirus (CMV) infection due to the presence of mucosal ulcers.

The patient was admitted to hospital under the gastroenterology service. The patient's CRP decreased to 99 mg/L over the following week, but then peaked at 147 mg/L approximately three days later. During this time, he continued to have more than ten bowel movements per day. A repeat colonoscopy was performed the next day, and demonstrated extremely friable mucosa, loss of vascularity, deep ulceration, as well as possible pseudomembranes. Oral vancomycin was started to empirically cover for *Clostridium difficile* (*C. difficile*). Fecal studies and C. difficile toxin done at that time eventually resulted as negative.

The patient's symptoms failed to improve. A Computed Tomography (CT) scan was performed on the subsequent day. It demonstrated pan–colitis, diffuse colonic wall thickening, and a transverse colon full of gas, which was dilated to 7.5 cm. There was a large amount of intra–abdominal free air noted, mostly peri–hepatic. Trace amounts of free fluid were noted in the abdomen. The patient was then assessed by general surgery and taken to the operating room for a total colectomy. The procedure was uncomplicated and the patient was sent to recovery in stable condition.

Pathology Findings

The gross pathology specimen demonstrated diffusely friable mucosa with deep ulcerations. Areas of hemorrhagic tissue were apparent in the ascending and transverse colon. The transverse colon was dilated at approximately 7.5 cm while the rest of the colon was of normal diameter.

Microscopic examination demonstrated friable tissue with areas of hemorrhage and signs of chronic inflammation. However, no CMV inclusion bodies or pseudomembranes were identified.

Discussion and literature review

Ulcerative colitis is a subcategory of inflammatory bowel disease affecting several million people annually.[1] At this point in time, the exact cause of ulcerative colitis remains unknown, and is likely due to a combination of environmental and genetic factors.[2] Any patient presenting with constant, bloody stools, abdominal pain, and distention should raise suspicion for ulcerative colitis. An appropriate diagnosis of ulcerative colitis is dependent on ruling out Crohn's disease and other causes of colitis.

The differential diagnosis includes infectious colitis, ischemic colitis, radiation colitis, intestinal tuberculosis, and inflammatory bowel disease, including Crohn's and ulcerative colitis.[3] After an appropriate history and physical exam, the workup consists of a standard blood count and inflammatory markers to assess for elevated leukocytes and erythrocyte sedimentation rate (ESR) or CRP. Stool studies including ova and parasites, gram stain, and culture should be used to rule out infectious causes. Plain radiographs may demonstrate mural thickening, and in more serious cases, thumbprinting. Double–contrast barium enema provides greater detail and may demonstrate ulcers and loss of haustral markings, but is contraindicated if there is risk of perforation, such as in acute colitis. CT scan of the abdomen would display similar findings to contrast enema but has limited sensitivity in early colitis. It is, however, very useful in ruling out other causes of colitis in the differential diagnosis.

If there are no signs or findings indicating infectious, ischemic,

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or radiation colitis, the workup may then focus in on inflammatory bowel disease. Initial serum studies may include p–ANCA and ASCA, which have been noted to be elevated in ulcerative colitis and Crohn's, respectively.[4] However, a high incidence of false positives prevents the use of these markers as final diagnostic tools. Abdominal imaging may demonstrate mesenteric fat stranding, thumbprinting, colonic dilatation, and with barium, the "string sign" in Crohn's disease.[5,6] Colonoscopy serves to assess the gross appearance of the colon, which may differ in ulcerative colitis and Crohn's. Biopsies for histopathologic analysis would also be taken during colonoscopy.

Ulcerative colitis demonstrates an inflamed colon limited to the mucosal layer. There could be associated loss of vascularity and ulceration. The lesions usually begin distally and progress proximally, in a continuous fashion. Crohn's would demonstrate transmural inflammation, with regions of inflammation separated by regions of normal colon, termed "skip lesions". Fistulas and abscesses may also be present. Histopathologic analysis of ulcerative colitis may reveal diffusely inflamed mucosa with associated crypt abscesses, micro–ulcerations, and inflammatory pseudopolyps. Crohn's disease may demonstrate focal areas of inflammation with associated granulomas. Histopathologic investigation may also reveal signs of superimposed infection such as pseudomembranes and CMV inclusion bodies. It should be kept in mind that microscopic analysis of inflammatory bowel disease is imperfect and it is not always possible to differentiate between Crohn's and ulcerative colitis. Ultimately, differentiation of ulcerative colitis from Crohn's depends on a combination of history and findings from the workup.[6]

Treatment for ulcerative colitis depends on disease severity.[7,8] The goal of treatment is to attain remission during acute flares and to maintain this remission with long–term agents. Mild to moderate disease is usually managed with oral and/or topical 5–ASA. If refractory, prednisone may be added to the treatment regimen. If disease continues to be refractory, mercaptopurine–6 and azathioprine may be trialed. Severe disease may require biologic treatment with infliximab (Remicade), or surgical treatment with colectomy. Acute flares of severe disease should be treated with IV cyclosporine or methylprednisolone in hospital with the goal of transitioning to oral therapy. One should also keep in mind that immunocompromised patients, such as those with ulcerative colitis, are at high risk of developing superimposed infections such as CMV or C. difficile.[9,10] Antimicrobials and antivirals should be added to the treatment regimen if history and workup demonstrate findings of infection such as fever, tachycardia, bloody or loose stools, leukocytosis, positive blood or stool cultures or signs of bowel wall thickening on imaging. Acute disease that does not improve after 48-72 hours of IV treatment requires urgent colectomy. Indications for surgery in acute ulcerative colitis include failure to respond to medical therapy, fulminant colitis, toxic megacolon, perforation, or stricture.[11]

Although the absolute risk of perforation in acute ulcerative colitis remains low, this complication is well documented with several reported cases.[12-15] The risk of bowel perforation after colonoscopy is increased in patients with inflammatory bowel disease.[16] Colonoscopy during an acute flare of ulcerative colitis may increase this risk further. Other risk factors associated with colonoscopic perforation include female sex, advanced age, severe colitis, use of corticosteroids, presence of notable comorbidities such as cardiovascular, hepatic, metabolic and other GI disease, as well as stricture dilation. Lower–caliber endoscopes have been suggested as a possible solution to this. Pneumoperitoneum after colonoscopy is generally associated with bowel perforation, and the incidence of benign pneumoperitoneum is exceedingly low. The patient presented here underwent colonoscopy the day before pneumoperitoneum was noted. However, the transverse colon had been distended several days prior to this. It is impossible at this point to determine whether the perforation was strictly due to disease progression or a complication of colonoscopy. Regardless, it will be important to monitor this patient carefully, as post–operative complications following colectomy for acute ulcerative colitis may be as high as 27.0%.[17] Though colonoscopy remains an invaluable tool to monitor the progression of inflammatory bowel disease, patients at high risk of perforation should be identified and managed accordingly. Guidelines for the prevention of colonoscopic perforation have been proposed.[16] Physicians managing patients with acute ulcerative colitis should be well versed in such guidelines and aware of risks such as bowel perforation given its immediate life–threatening acuity.

Conclusion

Acute presentation of ulcerative colitis is a potentially life–threatening medical emergency. First–line therapy consists of medical treatment to induce disease remission in order to transition to oral maintenance therapy. Empiric antibiotic and antiviral coverage should be added for suspected superimposed infections. Complications of acute ulcerative colitis include bowel perforation and toxic megacolon. Bowel perforation after colonoscopy occurs at an increased frequency in these patients. Extra precautions should be taken when working with these patients in an attempt to reduce the risk of such perforation. The ultimate treatment for perforation is urgent colectomy.

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Surgical innovation in the cold war era: Gavril Ilizarov and his apparatus as a device for external fixation and limb lengthening

Boluwaji Ogunyemi[1]
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Abstract

Gavriil Abramovich Ilizarov [1921-1992] was a researcher and innovator of orthopedic surgery. In the setting of the Second World War, he was forcibly evacuated from Crimea where he studied medicine. He finished his studies in Kazakhstan before working in rural Siberia. Being positioned behind the Iron Curtain complicated the dissemination of the surgeon's apparatus to North America. From rudimentary materials in rural Siberia, Ilizarov pioneered an external fixator used to lengthen limbs and treat comminuted fractures.

Ilizarov's early years and education

Gavril Ilizarov was born in Białowieża, Poland (present day Belarus) in 1921. In childhood, he sustained a bout of food poisoning and, upon his recovery, developed a deep and persistent interest in human illness.

Ilizarov's father died when Gavriil was very young, resulting in tremendous economic hardship for his family. There was little support for Ilizarov to attend school and, consequently, his formal education was delayed until age 11. By age 16, Ilizarov had completed the equivalent of ten years of education in five consecutive years. In the setting of the Second World War, Ilizarov was forcibly evacuated from Simferopol, Crimea where he studied at the Simferopol Medical Institute. Finally, he would finish his studies in Kzyl–Orda, Kazakhstan and, at the age of 22, was awarded his medical degree in 1943.

In 1944, Ilizarov returned to a rural setting when he was assigned to practice general medicine in Dolgovka, Siberia, a remote region that had previously been used for the exile of Tsars and their families.[1] Ilizarov came across a shaft–bow harness connecting a horse to its carriage through shafts. This served as inspiration and he attempted to incorporate this mechanism into a prototype to repair fractures. Before ever testing on a living subject, Ilizarov first created an apparatus based on the shaft–bow harness to "treat" broken broomsticks. He made several rudimentary versions of the device, trying each time to further reduce mobility of the broken broomstick. Ilizarov would eventually seek help from a local metal–worker to fashion ring–shaped wires that would be suitable for use on human limbs.

The Ilizarov apparatus became a system of external fixators consisting of stainless steel rods, rings, and kirschner wires. The method was distinct from conventional external fixators in that the apparatus encased the limb and formed an external cylinder around it. The circular construction afforded early weight bearing for patients since it provided greater support than monolateral fixators. A key biophysical element was that the superior rings of the apparatus allowed force to be transferred from the bone distal to the fracture site, through the external frame (bypassing the fracture site), directly to the bone proximal to the fracture. Although its initial application was to effectively stabilize severe fractures for healing, Ilizarov realized that the apparatus could also be used to lengthen a limb. The Ilizarov external fixator apparatus' use for this purpose relied on the principle of distraction osteogenesis; when two ends of a bone are distracted but the periosteum remains intact, new bone is laid down to fill the space. This regeneration of bone was applied to correct limb length discrepancies.[2]

Ilizarov's studies proved that the ideal setting for new bone formation consisted of a low–energy osteotomy followed by one week of latency and a distraction of the bone at a rate of one mm/day in four divided increments.[3]

New beginnings: Ilizarov moves to Kurgan and creates the apparatus

In 1950, Ilizarov moved to Kurgan, Siberia. Practicing in this larger center allowed Ilizarov to develop his apparatus and broaden its scope.

Though formally trained in general medicine, Ilizarov was promoted to Director of the Kurgan Research Institute for Experimental Orthopaedics and Traumatology because of his experience with his innovative apparatus. He chose former Russian soldiers in the Second World War as his initial patients. Ilizarov was disheartened by the time required for severe fractures to heal and wished to use his technique in an effort to repay veterans for their service.

In 1964, Soviet high jumper and Olympic champion Valery Brumel found his career cut short after a severe automobile accident. Brumel sustained comminuted fractures resulting in the near complete loss of the use of both legs. In desperation, Brumel sought help from Ilizarov and was successfully treated in 1967.

Knowledge transfer: The Ilizarov Apparatus comes to the western world

At the time, University of Toronto orthopedic surgery resident, Dror Paley, was motivated to learn of this new technique and bring its benefits to North America. But tensions in the Cold War era Soviet Union made it extremely difficult for people from the Western World to gain access to this "closed" Soviet city. In 1986, Illizarov and other Soviet–based surgeons hosted an International Conference on Transosseous Osteosynthesis, giving Paley the perfect justification to enter Kurgan.

Ilizarov felt it was important to disseminate his method to an American audience but was simultaneously wary of not receiving

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credit from American scientists and clinicians, especially given the air of secrecy between the two nations. Paley helped to assuage these tensions by being able to communicate with Ilizarov in Russian. Since Ilizarov was more willing to share the confidential details on the use of his apparatus in the absence of an intermediary translator, Paley enjoyed greater access to the intricate details of mastering the technique. As well, being from Canada, as opposed to the United States, made him less threatening. For Paley, learning Russian provided an opportunity to make sense of many of Ilizarov's original documents.[4]

The Ilizarov procedure of Transosseous Osteosynthesis was alive and well by the late 1980's.[3] When Ilizarov eventually went to Rome in 1982 to lecture on his innovation, the Ilizarov apparatus had already began to acquire global fame. Italian surgeons dubbed Ilizarov "The Michelangelo of Orthopedics."

Ilizarov Apparatus in the 21st Century

Ilizarov was a rigorous and thorough researcher and surgeon. As outlined by Baker and Offut,[5] hundreds of hours are required before a surgeon is considered adept at employing Ilizarov's external ring fixator technique. Preassembling specific external frame designs proves especially time–consuming.[5] Today, the Ilizarov external fixator is primarily used to correct leg length discrepancies. Infection of the pins is a common complication of the apparatus, limiting its use in stabilizing comminuted fractures. Sometimes, patients must maintain the apparatus for several months and the months of required rehabilitation necessitates a motivated patient.[2] Dror Paley, one of Ilizarov's earliest trainees, is now the medical director at Florida's Paley Institute. Here, the Ilizarov apparatus is employed to correct limb length discrepancies due to skeletal dysplasia, congenital short stature, as well as achrondroplasia and other forms of dwarfism. In adults, the apparatus is most often used to manage post–traumatic limb length discrepancies.[3]

Hero of Socialist Labor

Constantly absorbed in his work, Ilizarov had been known to regularly work sixteen–hour days, from ten in the morning until two o'clock the following morning. Ilizarov had been bestowed the rare honor of Hero of Socialist Labor in 1981 and was named a member of the Russian Academy of Sciences ten years later. He was awarded the Lenin Prize in 1979. This prestigious award was given to an individual for significant contribution to any of the fields of science, literature, arts, medicine, architecture, or technology. In 1992, the decorated surgeon, researcher, and pioneer, died of heart failure at the age of 71 in his hometown of Kurgan. The Ilizarov Centre for Orthopedic Surgery in Kurgan has been repurposed to focus on the surgical correction of congenital limb abnormalities. A scientific journal in honour of Ilizarov was created shortly after his death entitled "Genii Orthopedii" (Orthopaedic Genius).[4]

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Social media in medical education: A case for a preparation approach

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Abstract

The response to social media by professional organizations in Canada focuses largely on preventing professional misconduct. The author discusses his experience with social media in medical school and details positive uses of social media in the literature. Education in social media and discussion around the technology should recognize and promote positive uses of social media to empower physicians to use the technology for health advocacy and promotion.

My journey into medicine has just begun, and already a common theme is emerging from my colleagues and professors: beware of social media. It comes up again and again from guest lecturers, speakers at our white coat ceremony and a lecture in our curriculum dedicated to online professionalism. The tone is sombre: be vigilant lest your professional career is whisked away by a Facebook photo gone wrong. I argue that teaching students to effectively use social media to connect with their family and peers, disseminate accurate medical information, and advocate for their profession would foster a more constructive dialogue surrounding social media usage by medical students.

The focus on potential harm of inappropriate social media use—both by physicians and patients—is well deserved. There have been many instances of unprofessional conduct by medical students and physicians documented in the literature.[1, 2] In response, the Canadian Federation of Medical Students (CFMS) produced the "CFMS Guide to Medical Professionalism: Recommendations for Social Media", which details guidelines intended to protect students from unprofessional conduct online.[3] The tone of the document prioritizes the protection of medical students in the online world. Similarly, the Canadian Medical Association (CMA) released a document that reminded physicians that social media is a public platform and the same rules that govern physicians having a conversation in a crowded cafeteria apply to posts on social media.[4] The tenor of these discussions is geared toward preventing professional misconduct, rather than increasing health literacy, advocating effectively, or connecting with colleagues. The CanMEDS roles of health advocate and communicator can be applied to social media, but this dimension receives cursory attention from the CFMS and the CMA.

Already in my medical education it is clear that social media is the primary mode of communication between my classmates. Whether organizing fundraisers or sharing student–made study resources, social media has become an integral part of my medical school experience. Specialty interest groups have Facebook pages that make it easy to connect with the next suturing workshop or neurology guest lecture. Furthermore, connecting with my colleagues over Facebook helps us organize social events that foster collegiality and maintain a healthy school–life balance. My peers share articles and news stories they find interesting, generating dialogue about issues like indigenous health or the strengths and weaknesses of various clinical trials. The ease of communication between colleagues about health initiatives is a major benefit of social media that will allow my class to stay connected as we progress through our careers.

Social media is also a valuable tool for practicing physicians. George and colleagues provide a compelling argument for how evolving privacy settings are allowing physicians to create "circles" of patients and control what information is disseminated to them, such as, "guidance on keeping blood pressure low, reminders of how to prepare for doctor's visits, postings about the availability of seasonal vaccines, or even links to salient medical research, archives of healthy recipes, or podcasts about innovative exercise programs."[5] Another example of positive social media use is Alliance Urgent Care & Family Practice in Colorado, where they promote health by posting information on flu shot clinics or updated research on the human papillomavirus vaccine for males.[6] These examples reinforce the idea that social media is built to connect people and is a valuable route for physicians to stay engaged with their patients.

Another benefit that social media gives physicians is the opportunity to curate their online image in a positive way.[7] Regardless of subscription to social media, there is information available online about a physician's education, training and disciplinary action from professional registries.[8] A positive social media presence in the form of a blog or website gives the physician a voice in their online identity and can create, "understanding, reflection, and greater appreciation of the patient–physician relationship."[9] This online identity can then be used as a channel for health advocacy by engaging members of parliament, community groups, and other physicians in online dialogue about health. Social media is a powerful communication tool and the emphasis should be on using it to benefit the profession rather than censoring your material to avoid litigation.

The tone of the conversation around social media is important, as evidenced by Lerner when he states, "[the] emphasis on the perils of social media could also have the unintended effect of condoning unprofessional activities in a 'don't ask, don't tell' sort of way."[10] This analysis suggests the protection approach to social media posits that as long as it is not documented on social media, unprofessional conduct may escape notice and is, therefore, acceptable. Not only does an emphasis on consequences neglect the benefits outlined above, but it also reinforces a division between persons and their identity as a professional, a division that suggests a professional social media presence may be an effective substitute for a professional. While a positive approach to teaching online professionalism does not eliminate this risk, it reduces the legitimacy of this line of reasoning by insisting that the CanMEDS roles of health advocate and professional extend

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to social media, as they do to medical students in a public setting.

One cannot expect every medical student will use social media as an advocacy tool, or that every medical student will have social media. For those who are willing, however, discussion of social media should weigh the benefits and risks of such advocacy and provide suitable suggestions for mitigating risk while maximizing the potential benefit. The focus of professional organizations and the literature surrounding social media and medical students on dangers of social media neglects the evidence that social media can be used effectively by medical students and physicians to connect with patients and colleagues,[5, 6, 7, 8, 9] leaving the impetus to individuals to decide if they want to "risk" using social media. Social media education in medical school should prepare students to use these technologies in a way that promotes health among health professionals, their families and friends, and the general public.

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The doctor is online: An introduction to text–based telepsychiatry

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Abstract

Text-based e-counselling has the potential to expand and improve the delivery of telepsychiatric services. Despite the loss of visual connection in patient-physician interactions, text-based communication offers many unique advantages. Patients often feel more comfortable with self-disclosure when communicating online and through text. Online mediums are also more accessible for patients who may face geographic, financial, or social barriers to receiving traditional in-office psychiatric care. While text-based telepsychiatry is highly cost-effective, concerns regarding privacy, security, and emergency use must be taken into consideration for future implementation.

Introduction

With digital communication quickly becoming the social norm, mental health professionals have begun to explore its potential for patient counselling. The practice of telepsychiatry uses telecommunications technology to address the growing demand for more accessible and efficient alternatives to in-office visits.[1] The goal of telepsychiatry is to enhance existing capacities, rather than to replace traditional delivery of services.[2] Telepsychiatry programs are currently available in all Canadian provinces, with the majority of models using videoconferencing to connect with patients online (e.g., SickKids TeleLink Mental Health Program, CAMH Northern Psychiatric Outreach Program).[3-5] As the field of telepsychiatry continues to grow, additional modalities for communication should be considered. Notably, text-based e-counselling remains unexplored despite widespread use in non-medical online therapy;[6] its role in the psychiatric setting has yet to be established.

Therapeutic communication

Unlike conventional therapy, text-based e-counselling relies on written communication between the patient and psychiatrist. Interactions can be synchronous, with little time gap between responses (e.g., real-time chat rooms), or asynchronous, where a time delay is expected (e.g., e-mail, web forms).[7] Synchronous counselling allows for greater spontaneity, prompted disclosures, and reduced recall bias in patient responses.[8,9] Alternatively, asynchronous counselling removes the pressure to reply instantly, giving patients time to edit their responses and therefore a greater sense of control.[10,11] By allowing patients to choose when and how often to share their experiences, text-based modalities may yield important information otherwise missed during scheduled appointments. This could prove particularly useful in capturing transient mental states, such as fluctuations in mood or cognition. Furthermore, having a written transcript enables both parties to revisit and remind themselves of ideas expressed in previous sessions.[12]

Some clinicians are concerned that the absence of face-to-face interaction and non-verbal cues could undermine communication during therapy.[13,14] However, these losses are partly offset by the online disinhibition effect, a well-studied phenomenon wherein people self-disclose to a greater extent online than in-person.[13,15,16] Ambiguity of written tone can also be improved by paying attention to elements of the text that convey emotion, including emoticons, emotional bracketing, purposeful use of punctuation, and verbosity.[10,14] The lack of visual connection may even facilitate disclosure, as patients often find it easier to discuss intimate, stigmatizing, or embarrassing subjects through writing.[8,9,16,17] Multiple systematic reviews have found text-based e-counselling to be equivalent or better than face-to-face sessions in terms of quality of the therapeutic alliance, with consistently high patient satisfaction.[18-20] The reviewed evidence also suggests that text-based interventions have similar effectiveness to face-to-face therapy in improving treatment outcomes.[19,20] However, several components of the psychiatric examination cannot be conducted through text, particularly those that require physical observation (e.g., appearance, behaviour, speech, affect). Therefore, the role of text-based e-counselling would be most appropriate only as an adjunct to face-to-face assessment when considering diagnosis or treatment.

Accessibility

Telepsychiatry presents an accessible alternative for patients who otherwise face barriers to receiving traditional in-office psychiatric care. By eliminating the need for travel, online services can more easily reach individuals with mobility limitations, rural residents, incarcerated individuals, and those who cannot afford transportation.[8,12,21] Web resources that are available at any time of day, such as e-mail, offer the additional convenience of being accessible outside of regular work or school hours, as well as for immediate use during times of distress.[8,12] The accessibility of telepsychiatric services, however, is ultimately determined by the provider, who selects the hours and mediums through which they can be contacted.

Differences in social functioning can make the traditional psychiatric setting feel inaccessible to some users. Patients with social anxiety, shyness, or embarrassment about their mental health concerns may avoid services that demand face-to-face disclosure or interaction.[8,12] Some individuals with autism prefer communicating online through text, as it removes the expectation for certain social cues and allows more time for articulating thoughts.[22] It can also be conducted in an environment without sensory overstimulation, particularly from eye contact and noisy chatter.[22] Text-based telepsychiatry may offer a more comfortable medium for these patients to seek and receive care.

Privacy concerns may persuade some individuals to seek online forms of counselling, while causing others to avoid it. Reasons for choosing e-counselling over in-office treatment include wanting to reduce the risk of being seen in a psychiatrist's office, or being discovered by a family member.[8] Adolescents may be particularly concerned with having to disclose mental health concerns to their family if they are unable to independently access psychiatric services.[11] When compared with videoconferencing or telephone, which require the user to speak aloud, typed text provides a more discreet interaction in shared spaces.[11,17] However, some patients still feel unsafe conducting

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any online sessions in the vicinity of curious family members, while others perceive an inherent lack of privacy in disclosing sensitive material over the Internet.[8] For example, users might worry about the existence of transcripts that could be seen by a spouse or employer.[8] Depending on the individual's personal ideas and concerns regarding privacy, text-based e-counselling may appear more or less accessible than traditional face-to-face counselling.

Cost savings

Although implementing telepsychiatry requires initial investments in software, hardware, and infrastructure, savings in transportation greatly reduce overall system costs.[23] This is especially true when providing for rural and geographically isolated communities. A randomized controlled trial conducted in Thunder Bay, Ontario found that telepsychiatry eliminated the travel and accommodation expenses required for face-to-face consultations.[24] Even accounting for the costs of videoconferencing equipment and bandwidth usage, the average telepsychiatric consultation cost 16% less compared to face-to-face delivery, with savings of $50 per visit.[24] Simpler, low bandwidth text–based technologies would likely incur even fewer technical expenses. Correctional facilities are another setting in which the use of telepsychiatry has generated savings ranging from $12,000 to over $1 million per institution, owing largely to reduced transportation costs for physicians and inmates.[23] Besides eliminating the need for travel, telepsychiatry has demonstrated cost savings through more efficient use of physician time, decreased overutilization of other medical services, increased medication adherence, and faster diagnosis via reduced waiting or consultation time.[9,23]

Other considerations

There are several additional considerations for implementation. Security and confidentiality may become an issue, as e-counselling records must be encrypted to protect against information theft.[25] It is also difficult to verify the user's identity through a text-based interface; patients could intentionally misrepresent themselves online or be impersonated by anyone with their login credentials. Other technologies sharing similar vulnerabilities, such as electronic medical records and patient portals, have led to the development of secure networks and user verification systems to address these concerns.[26] Furthermore, secure e-mail platforms for telepsychiatry already exist and have demonstrated good uptake across several institutions for their familiarity and ease of use, incurring little to no training costs.[27]

Long distance communication introduces greater unknowns about the patient's immediate status, which may complicate the management of emergency situations. This underscores the importance of discussing mutual expectations before initiation. For example, clinicians may not know whether sudden disconnections during synchronous chat are due to technological failure or a developing patient crisis.[28] On the patient's end, such a disconnection could be perceived as abandonment if not discussed ahead of time.[29] Clinicians should also verify the patient's location to facilitate access to emergency services if required.[25] This is especially difficult in asynchronous conversation, as the patient may have changed locations or engaged in harmful behaviour by the time the clinician views new messages. Thus, physicians should be cognizant of the limitations of text–based interventions for patients at higher risk of self–harm.[21] While emergency management guidelines have been established for videoconferencing telepsychiatry, none specifically exist for text–based modalities;[30] however, since both models are affected by distance, recommended use will likely follow similar principles.

Perhaps the most important consideration in the adoption of telepsychiatry is clinician uptake. The American Psychiatric Association recently updated its policy to approve telepsychiatry as a validated and effective delivery system.[31] While the Canadian Psychiatric Association has yet to follow suit with an official statement, a recent survey of Canadian mental health professionals demonstrated an overall positive attitude toward the use of telepsychiatry services.[32] These trends are conducive to the widespread uptake of telepsychiatry technology; however, acceptability regarding text-based modalities, in comparison to the standard prototype of videoconferencing, has yet to be specifically delineated.

Conclusion

Text-based modalities show promise in expanding the delivery of telepsychiatric services, offering an effective, accessible, and cost-effective approach to therapy. More research is needed to establish the role of text-based telepsychiatry beyond the scope of counselling and determine whether it can facilitate diagnosis as well as prescription. At present, text-based therapy should be used to supplement rather than replace face-to-face examination, which can help to increase uptake of mental health services among individuals who may otherwise have limited access. Within the larger paradigm shift towards modernized, technologically innovative care, text-based telepsychiatry represents an avenue of untapped potential.

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Is Canadian healthcare lagging behind when it comes to technological literacy?

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Technology is transforming our world of medicine faster than medical professionals can keep up with it. When tasked with running a busy clinical practice, technological literacy often falls low on a physician's list of priorities. This lack of literacy among current physicians is causing a lag in the uptake of useful technologies that can revolutionize medicine in Canada. A bright spot is that Electronic Medical Record (EMR) adoption has increased from approximately 25% in 2007 to 75% in 2014 across Canada.[1] EMR refers to a digitized version of a patient's paper chart. Electronic Health Records (EHR) is a term that describes the entire software that organizes, stores, and shares patient data over a network.[2] The non-compatibility among EHR software between health networks has been one of the Canadian healthcare system's biggest downfalls. As large companies such as Google and Apple become more integrated in our lives, what happens if one of these large companies does EHR better than the public system? With innovative technologies around the corner, steps to make future physicians more current on the world of technology in medicine are warranted.

Canada's "slow and silo-style" adoption of EMR

In the early years of EMR during the 1990s, its uptake was particularly slow.[3] A dearth in financial incentives for physicians to pay the upfront cost to switch from paper to EMR, along with the losses associated with incorporating EMR into the workflow of a medical practice were often blamed for this slow uptake.[4] The adoption rate in Canada was noticeably lower than its developed nation peers during this early period.[5] With its focus solely on adoption, much of Canada's shift to EMR was developed with a "silo approach" and information technology (IT) systems were incompatible with sharing patient data with each other. In response to this widespread issue, Canada Health Infoway was launched in late 2000 with an initial investment of $500M to streamline the EMR across Canada towards interoperable EHR (iEHR).[6] iEHR is an integrated EHR that allows the sharing of patient data across the healthcare continuum. Although they have planned out a pan-Canadian iEHR action plan many years ago, it is only in recent years that provinces are moving toward iEHR, and this progress is variable. A review published in 2016 stated that only 58% of physicians are reporting access to iEHR data.[7] If just short of half of physicians are being left behind in iEHR access, one must wonder how well-connected our healthcare is at a provincial level.

Traditionally, each province and territory is allocated a certain budget for their own healthcare system. Within each province or territory, a global budget is the most common funding structure, where health authorities are allocated an operating budget for their year.[8] Due to this segmented approach, it is possible that health networks, even within provinces and territories, have issues with exchanging patient data with one another. This is affirmed by an announcement by the province of British Columbia (BC) stating that an $842M investment will be made to integrate and modernize EHR between Vancouver Coastal Health (VCH), Provincial Health Services Authority (PHSA), and Providence Health Care (PHC).[9] Canada Health Infoway also states that each province and territory is responsible for developing their own iEHR solutions.[10] When provinces and territories create iEHR independently without a plan to connect them, further healthcare dollars may be spent to retrospectively connect each provincial health system with one another.

Streamlined EHR with nationwide share-ability

Many start-up companies have looked into designing iEHR software that allows for simple and easy patient data sharing. Practice Fusion is an example of an EHR start-up in the United States (US) that has achieved this. Their website claims to have processed 56 million patient visits in 2014 which is equivalent to 6% of all ambulatory visits in the US.[11] Their software is free, and has a well-connected user base, which allows for the sharing of EMR to anywhere across the US. A nationwide connected iEHR similar in scope to Practice Fusion could be beneficial for Canada in numerous ways. For example, centralizing waitlists has been shown to cut down on waitlist times due to streamlining waitlist management in countries such as Portugal.[12] Centralized EHR could also facilitate the sharing of patient information between universities across the country for larger scale research trials, paving a way for big data to play a larger role in medicine in the future.

Implications of organized EHR on big data medical research

Google ventures led a $130M round of funding for a cancer data start-up named "Flatiron". Flatiron is a cloud-based cancer data start-up that aims to organize the entire cancer treatment process on one single EHR and connect cancer centers all across the US. Their pitch is that data for 24 out of 25 cancer cases is not kept in an organized manner, and that we should be building knowledge on every cancer case on a common platform in a HIPAA-compliant manner to fight cancer. This company looks to analyze this patient data in multiple ways to gain deeper insights into clinical decisions. For one, they claim that their platform will make it easier to identify candidates for large scale research trials. Secondly, they claim that their software will be able to pull up cases that are most relevant to the patient at the point of care.[13] If made HIPAA-compliant, consulting a database of potentially millions of patients for similar cases could help physicians find highly-specific information about drug treatments that worked better or worse for a similar type of patient. A software this powerful has potential to create a more personalized approach to oncology and potentially give us data to make better choices with respect to chemotherapy treatment.

Although Flatiron has potential, their company's structure raises concerns regarding how patient data is used and monetized. For one, they claim that their platform will allow "life sciences" companies to get an unprecedented view of how their drugs are used in the real world.[13] One must wonder if this patient data will be sold to pharmaceutical

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companies and whether this is ethical. Additionally, if a company like Flatiron is owned in majority by Google, who has a reputation for selling large amounts of data to marketing companies, conflicts of interest could arise in the future.[14] Canada should look to companies like Flatiron for ideas about how patient data can be leveraged to the benefit of everyone, but look to do so in a way that is transparent, ethical, and compliant with patient safety standards.

State of BC's physician leadership in the face of a technological revolution

A McKinsey report states that one of the potential key risk factors for BC's $842M EHR integration project is that there is not enough physician and health care provider involvement.[9] The EHR integration project faced some setbacks when IBM, the contractor heading the project, and the province of BC parted ways. The project has since been picked up by Cerner. A transition period was required to handover the project, causing a delay in the project's timeline and $190,000 spent in legal and mediation fees.[15] With a more technologically and project-minded physician population, risks of this nature would be mitigated in future IT renewal projects. Canada appears to be lacking in physician leadership who is well-acquainted with integrating technology in medicine. A lack of leadership could be addressed by educating medical students on technological literacy. The Sauder School of Business at the University of British Columbia (UBC) offers a course called Technology & Entrepreneurship (BAEN 506/APSC 541) that guides practical aspects of identifying a problem and planning, building, marketing, as well as funding a technologically-based solution for it. However, the 2015-2016 academic year was the last year that the course accepted medical students. Courses for medical students such as these should be encouraged by medical curricula, as they will create physician leaders who are technology-savvy and able to imagine and create technological-based solutions to systemic healthcare problems in the future.

Canada's fate and EHR

Healthcare is changing due to advances in IT. While the developed world innovates with EHR, Canada could possibly lag behind again if it does not keep up with the growing global demand for technological-modernity. To make a complete switch-over to a single iEHR transnationally would likely be too costly and disruptive to workflow, however at the same time Canada should be looking further into how technology and data can be leveraged to improve medicine when planning IT projects. This foresight requires knowledge of the healthcare system along with IT. Thus, medical curricula should consider technological literacy for physicians as an investment in the future of Canadian healthcare. Although not discussed here, professional development run by technology-industry leaders could also help to improve the technological literacy among Canadian physicians. A technologically-educated population of physicians will facilitate better choices regarding health information systems at the provincial and federal level.

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A journey to Mars: The medical challenges associated with deep space travel and possible solutions

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In the summer of 2016, the Canadian Space Agency began accepting applications for the next generation of Canadian astronauts.[1] To date, only twelve Canadians have ventured beyond the limits of our atmosphere, five of whom were medical doctors.[2] A physician's mindset is calibrated for high–stakes decision–making and is useful for making health decisions in a hazardous extraterrestrial environment. To some degree, the knowledge base that physicians bring to healthcare on Earth can be translated to providing healthcare in space. However, the environment in space poses complex health challenges that are difficult to overcome even with continuous advancements in technologies.[3-5] Space agencies rely on technology for providing out–of–this–world healthcare to maintain the health status of their astronauts during space missions.[3,6]

While astronauts are in space, their bodies adapt to the new environment in ways that are often pathologic. Bone demineralization, cardiovascular dysfunction, and muscular atrophy are a few of the many physiologic responses to the pathologic microgravity environment.[3,5,7-8] Radiation exposure is another major hazard for astronauts. All of the above issues are exaggerated when considering a mission such as travelling to Mars.[6,9-10] While a great number of health challenges have been identified in space travel, constant technological advances are bringing humanity closer to its first interplanetary journey.[3,9,11]

The next major step for humans in space exploration will be to put an astronaut on Mars and bring them home safely. Fortunately, after landing multiple unmanned space craft on the planet's surface, many of the logistics of travelling to Mars are well–understood.[12] With NASA hoping to take astronauts to Mars in the 2030s, the largest barrier is in developing technology that will keep astronauts safe for an unprecedented amount of time in space.[13] The current record holder for longest duration of space flight is Valery Polyakov, who was in a near–Earth orbit for 14.9 months, and experienced great difficulty with walking upon his return to Earth.[14] Located approximately 50 million kilometers from Earth, it is estimated that a return mission to Mars would take approximately 30 months.[13,15] The amount of effort required to advance medical technology in order to facilitate such a journey is likely to necessitate terrestrial efforts. In the past, work by NASA has contributed to the development of many medical technologies such as MRI, CT imaging, and left ventricular assist devices.[16-17] Consequently, this commitment to advancing the physical reach of humans in space may have unforeseen benefits for physicians back on Earth.

The first step in ensuring astronaut safety is in the rigorous screening process prior to boarding any space craft. Astronauts undergo exercise, endurance, and strength testing, as well as preflight nutritional assessment and psychological interviews.[3] Astronauts must have healthy kidney function, and carry low risks of coronary artery disease.[3] Astronaut DNA is assessed preflight for any previous damage or signs of marked susceptibility.[6] To reduce astronauts' risk of radiation–induced cancer, NASA excludes smokers because of their underlying cancer risk.[6] Female and young astronauts are at a higher risk for radiation–induced cancer because of differences in body composition and expected longevity following exposure to space, respectively.[6]

In addition to the preflight testing, inflight testing will be an essential component for ensuring astronaut safety on a mission to Mars. A space craft can carry a limited supply of medical equipment for emergency situations and regular monitoring. In the past, this has included ultrasound machines, serum analysis technology, ECG, defibrillators, restraints, and over 190 medications.[3,18] During space flight, astronauts have regular meetings with psychologists, as well as checkups that include exercise tolerance tests, radiation monitoring, and blood chemistry assessments.[3] Despite the pre– and inflight health assessments, fully understanding the human body's complex adaptations to long term microgravity is an ongoing challenge for space agencies.

One of the better known health complications for astronauts is the risk of bone loss and muscle atrophy in microgravity. In accordance with Wolff's law, bone will remodel according to the stress, or lack thereof, placed on it.[4] In space, ten percent of proximal femur bone mass can be lost in six months, representing a rate of bone loss that is ten times greater than that seen in osteoporosis.[5] In addition, rapid bone resorption in space can cause an increase in serum calcium to levels that may predispose astronauts to kidney stones; however, as with other medical research conducted on space travelers, studies demonstrating this effect struggle with small sample sizes and have low power.[5] Despite such limitations, the trends toward musculoskeletal depletion noted in astronauts during and following space travel prompted space agencies to recognize that for longer duration missions, bone loss must be combated. This began with the use of aerobic exercise machines with relatively high intensity exercise regimens.[5] Despite these efforts, total bone loss was still reported at 0.35% per month, leaving astronauts struggling to adapt to life back on Earth with the full force of gravity on their skeleton.[19] With this knowledge, more studies have been conducted to determine ideal diets and exercise regimens for astronauts.[11] A recent study that prescribed resistance exercise via an Advanced Restrictive Exercise Device found that astronauts undergoing this regimen did not experience significant bone loss.[5] In order to achieve these results, astronauts performed 2.5 hours of physical exercise six days per week while in flight.[20] Additionally, the use of bisphosphonates has recently been suggested for astronauts because of their effects in slowing bone loss in bedridden patients.[11] Through the combined effects of these innovations, astronauts are able to significantly reduce their risk of bone loss, which is a key factor in long–duration space travel.

Despite the progress in methods to prevent bone loss, there are many more health–related challenges to overcome before safely sending humans to Mars. One such challenge is the risk of radiation

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exposure in space. To date, no astronauts have endured long–term missions outside of Earth's geomagnetic field, which protects us from high–energy protons called Galactic Cosmic Rays (GCR).[6,9] In years past, many biological specimens have been sent into space to test the impact of radiation.[21] In these studies, significant rates of anomalies and changes in reproduction have occurred, with more extensive damage affecting specimens provided with Earthlike pressurization and oxygen content, allowing normal metabolic activity to take place.[21] Consequently, this risk is well–known to space agencies, and steps are currently being taken to minimize risk for future astronauts. The first level of protection is in screening astronauts for pre–existing DNA damage or susceptibility.[3,6] The second level of protection is related to a moral decision to be made by space agencies regarding how much radiation is an acceptable risk.[6] Thus far, NASA has adopted the Occupational Safety and Health Act (OSHA) of American workers which limits astronauts to a maximum of a 3% lifetime risk of exposure–induced fatal cancer.[6,10] While the annual dose limit in the United States is 50 millisieverts (mSv), most workers, such as radiotechnicians, reactor workers, or pilots, only receive between 1 and 5 mSv per annum. Meanwhile, a six–month stay on the International Space Station can expose an astronaut to 80 mSv.[10] With current technology, NASA estimates that a 30–month mission to Mars within a 5g/cm2 aluminum structure would expose astronauts to over 900 mSv, far beyond safe or acceptable OSHA limits.[6,10,22] NASA is currently working toward technologies that can protect astronauts from GCRs for long–duration missions. A hydrogen–rich barrier is best suited to prevent damage from GCRs, and items such as water or household plastics have been shown to be effective in this regard.[9] However, using either of these for a layer of protection may be difficult given the other requirements of a space craft. Recently, NASA has created hydrogenated boron nitride nanotubes that are heat–resistant and hydrogen–abundant, meaning that they confer significant protection from GCRs.[9] NASA has also proposed that a type of radiation bunker be used in case of any solar flares that may arise during a mission.[9] This technology will be essential for future travel to Mars, as the atmosphere of this planet provides very little protection from radiative forces.[9]

Radiation and bone loss risks aside, there are many more impacts of microgravity on the human body that remain understudied. Changes in cardiovascular function are significant in astronauts, as their hearts adapt to pumping against less resistance in space.[7] Among returning astronauts, 85% failed a tilt table test due to cardiovascular deconditioning incurred in space.[3,7] Astronauts have also reported visual anomalies that may be a consequence of radiation exposure.[23] Additionally, approximately 52% of astronauts have reported back pain in space, and many can also experience fatigue.[3,8] Evidently, there is much to be learned in this field regarding the pathophysiology of these health problems, as well as possible solutions. However, with the advances made in the fields of bone density retention and radiation exposure prevention, it is feasible that technology will be developed to combat these other medical complications.

Space travel has always been a unique exercise of combining the best of human potential to conquer incredibly complex challenges. The collective action of humans in achieving travel between Earth and space has taught scientists and physicians about the impact of microgravity on human health. Very quickly bone loss, muscle atrophy, and radiation exposure were recognized as significant risks in space flight, and many steps have been taken to counteract these effects. More recently, far more complications have been discovered, including visual, psychological, and cardiovascular pathologies. The plans of major international space agencies to travel to Mars through unprecendented levels of radiation or durations of space flight intensifies the associated risk of all of these health complications. However, space agencies remain dedicated to finding solutions to these problems through development of radiation barriers, machines for preventing bone loss, specialized nutritional supplements, and more. Space medicine is an incredibly unique field of medicine necessary for enabling humans to discover our ever-growing collective potential. In space, just like on Earth, medicine is of ultimate importance, and health professionals play a key role in enabling humanity to put its first footstep on the red planet.

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Dr. Google: Navigating the world of online health information

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The influence of the Internet is so pervasive in Canada that online connectivity has become inescapably molded into many aspects of everyday life. Up to 89% of Canadian households are currently connected to the Internet, and social media websites rank among the most highly visited pages by Canadian Internet users.[1] In fact, Canadians are the most active Facebook users globally, with over 19 million users who log on at least monthly.[2] Due to the explosion in popularity of social media in Canada and across the world over the previous decade, the dynamics of Internet marketing have shifted, with an increasing proportion of marketers currently targeting social media users.[3] Coupled with the fact that many individuals often turn to the Internet as a major source for health information, these trends indicate that the average Canadian Internet user may be exposed to many health–related advertisements and biased sources of information, even during routine browsing of social media pages.[4,5] An awareness of these trends is helpful for healthcare professionals to better anticipate the types of information that patients might be exposed to, as well as to provide education and guidance on navigating the online world as an informed Internet user.

Basics of search engine optimization and online advertising

Online advertising has changed dramatically since the first classic rectangular banner ad went live in 1994.[6] In the present era, Internet marketers have increasingly focused on search engines as a means of reaching the largest potential pool of customers, and paid advertisements currently constitute a major source of revenue for search engines like Google and Yahoo.[7,8] These paid advertisements appear at the top of search engine listings above "organic" search results (i.e., the nonpaid search results), under headings such as "Ads" or "Sponsored". After search terms related to legal, educational, and financial services, search terms related to healthcare are among the terms with the highest average cost–per–click (CPC) rates, serving as a testament to the size of the online health industry.[9] Aside from sponsored search engine listings, Search Engine Optimization (SEO) strategies have emerged as another cornerstone of modern Internet marketing. Through SEO, webmasters make use of efficient keywords, tags, and titles in order to have their webpages rank highly in the organic results of major search engines.[10] When a search engine like Google indexes the content of a webpage, it uses an algorithm that analyzes the keywords and tags on that webpage to determine how highly that page will rank in its search results, regardless of the reliability of the information presented on that page.[10] An ongoing risk therefore exists that misinformation might be propagated via search engines. As an example, a recent study evaluating Google search results for simple queries that include the phrase "human papillomavirus vaccine" revealed that up to 27% of results contained highly dissuasive and/or factually inaccurate information about the vaccine.[11] As a result, Internet users must always be wary of both commercialized advertisements and the inadvertent promotion of misinformation that can occur when conducting online searches related to healthcare topics.

Next steps: Social media marketing

Following the rise of social media websites like MySpace and Facebook in the early 2000s, a broader arsenal of tools and options became available to Internet marketers than ever before. With the advent of marketing technology that made it possible to correlate Internet cookies from search engines like Google with cookies from social networking websites like Facebook, marketers soon gained the ability to display customized ads on social media websites based on a user's previous Google searches.[12] Social media advertising has grown exponentially in recent years, with revenue for these particular types of ads projected to reach $11 billion USD in 2017 in the United States alone.[3] Unfortunately, the rise of social media marketing has also ushered in new avenues of deceptive online marketing practices. For example, unscrupulous marketers might utilize fraudulent social media profiles to distribute biased product reviews, with recent conservative estimates placing the rate of such fraudulent reviews at approximately 15%.[13] This is particularly concerning given that research has indicated that Internet users might place more value on product reviews written by other online customers, compared with professional reviews written by experts.[14] These observations are of no small significance in the online health industry, where up to 42% of Internet users in the United States routinely search for diet and weight loss information, for example, and the annual revenue generated by the online vitamin and nutritional supplement market targeted to such searches is approximately $7 billion USD.[15,16] Considering these trends of consumer behaviour within a climate of Internet marketing practices such as SEO, customized social media advertisements, and fraudulent product reviews, it is evident that the uninformed consumer is particularly vulnerable to the tactics and manipulation of deceptive marketers when browsing health information on the Internet.

Web 2.0 and a new era of online health information

Although examples abound of inaccurate sources of online health information, healthcare professionals can, with a simple understanding of the basic workings of the Internet, begin to combat this problem and help their patients avoid falling victim to the veritable maze of deceptive marketing and unfounded claims that exist on the web. In fact, some physicians have even taken a proactive approach to this issue by establishing their own personal blogs and websites. As an example, internal medicine physician Kevin Pho founded KevinMD.com in 2004, a website which has grown to become a leading social media platform in the healthcare sector and currently receives contributions from over 2,000 authors.[17] An important feature of this website is that it embodies many aspects of so–called "Web 2.0", a conceptual term used to describe modern websites that include such features as user–generated content, interactivity, and connectivity with other social media

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platforms, among others.[18] Interestingly, a recent study examining the dissemination of vaccination information compared representative anti–vaccine and pro–vaccine websites and found that the anti–vaccine websites took advantage of more features of Web 2.0, including user connectivity and testimonials, relative to the pro–vaccine websites, which were mostly formal, encyclopedia–like resources.[19] Although the implications of these findings remain to be clarified through further research, it is conceivable, given the ongoing rise in popularity of social media, that the average Internet user might respond more favourably to health websites incorporating features of Web 2.0.[2] For instance, it has been suggested that the interactivity afforded by social media might be particularly conducive to engaging the public more effectively with specific topics such as health promotion.[20] Moreover, social media and Web 2.0 might resonate especially well with certain patient populations, such as pediatrics.[21] With this in mind, an opportunity exists for the establishment of more websites run by healthcare professionals, incorporating key features of Web 2.0, in order to temper the online pollution of misinformation that currently exists.

The fact that patients will seek health information online is an inescapable reality of the present era. Among many physicians, the traditional approach to this problem has often been to dismiss all sources of online health information as untrustworthy and to scold patients any time they confess to entering symptoms in an online search box. Rather than adopting this simplistic approach, it could be argued that modern physicians have a duty to take a more proactive approach and inform themselves about the Internet to understand the types of information that their patients will encounter. For physicians who are so motivated, helping to establish reputable sources of online, patient–friendly information that incorporate features of Web 2.0 and that will reach the largest audience possible could help to pioneer a new era of online health information. By this strategy, we might reach a day where reputable websites overshadow the commercialized and biased ones, and Dr. Google might become a trustworthy source of health information, rather than one to be avoided altogether.

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The University of British Columbia Medical Journal (UBCMJ) is a student-driven academic journal with the goal of engaging students in medical dialogue. Our scope ranges from original research and review articles in medicine to medical trends, clinical reports, elective reports, and commentaries on the principles and practice of medicine. We strive to maintain a high level of integrity and accuracy in our work, to encourage collaborative production and cross-disciplinary communication, and to stimulate critical and independent thinking.

Submission Guidelines

Articles are submitted online via our online submissions system, OJS (http://ojs.library.ubc.ca/index.php/ubcmj). For detailed submission instructions, please refer to the complete online version of the UBCMJ Guide to Authors, which can be found at www.ubcmj.com.

Author Eligibility

Authors must acknowledge and declare any sources of funding or potential conflicting interest, such as receiving funds or fees from, or holding stocks and benefiting from, an organization that may profit or lose through publication of the submitted paper. Declaring a competing interest will not necessarily preclude publication but will be conducive to the UBCMJ's goal of transparency. Such information will be held in confidence while the paper is under review and will not influence the editorial decision. If the article is accepted for publication, the editors will discuss with the authors the manner in which such information is to be communicated to the reader. UBCMJ expects that authors of accepted articles do not have any undisclosed financial ties to or interest in the makers of products discussed in the article.

In the interest of full transparency, no current members of the UBCMJ staff will be permitted to publish in the journal, except for those officially invited in a staff writer capacity to author a news piece or editorial. This policy is intended to limit the potential for conflicts of interest. All former members of the UBCMJ staff are exempted from this policy, as they will not have involvement in the workings of the journal at the time of their submission.

Author Originality

Authors must declare that all works submitted to the UBCMJ contain original, unpublished content and have been referenced according to the appropriate academic style. Written content that displays excessive similarity to previously published works, including works written by the submitting authors, will not be published by the UBCMJ. This policy is consistent with the UBC policy on plagiarism. Figures or images may be re-published in the journal, with permission from the original authors, for illustrative purposes. The UBCMJ editorial staff reserves the right to request revisions, to deny publication, or to require retraction of submitted or published work that contains clear violations of this policy.

Specific Submission Criteria

Academic Research

Research articles report student-driven research projects and succinctly describe findings in a manner appropriate for a general medical audience. The articles should place findings in the context of current literature in their respective disciplines. UBCMJ currently accepts both full length articles and research letters.

Written permission must be obtained from persons acknowledged in the article, and all co-authors and contributors must sign a disclosure agreement that accompanies the submission. Proof of ethics approval and/or research ethics board numbers must also be provided.

Reviews

Reviews provide an overview of a body of scientific work or a medical trend. Reviews may outline a current medical issue or give insight into the principles of practice of a clinical field. Authors may choose to review the etiology, diagnosis, treatment, or epidemiology of a specific disease. Articles may also provide a survey of literature dealing with philosophy and social science as it pertains to medicine.

Case and Elective Reports

Case Reports describe patient encounters in a clinical or public health setting. The case should provide a relevant teaching point for medical students, either by describing a unique condition OR by presenting new insights into the diagnosis, presentation, or management of a more common condition. All submissions to this section must contain a written copy of patient consent.

Elective Reports provide a specific description of the scope of practice of a medical specialty and/or training program, and recall the student's impressions and reflections during and upon completion of the elective.

News and Letters

This section includes articles that touch on current events in the field of medicine, significant medical advances, or brief summaries of research in an area. Note that submissions to this section do not require extensive elaboration on the methods or results of the review process.

Commentaries

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:

- Subjective pieces relevant to medical studies, life as a future physician, or the current social context of medicine.
- Clinical perspectives on an interesting research study or area of focus.

Correspondence

For any questions related to your submission, please contact the appropriate Section Editors.

Academic Research	(academic@ubcmj.com)
Case and Elective Reports	(reports@ubcmj.com)
Reviews	(reviews@ubcmj.com)
News and Letters	(news@ubcmj.com)
Commentaries	(commentaries@ubcmj.com)

The UBC Medical Journal is now accepting submissions for...

UBCMJ
Volume 9 Issue 1
Fall 2017

Personalized Medicine

The UBC Medical Journal is now accepting submissions for the Fall 2017 issue. The theme of the issue is Personalized Medicine – from fundamentals to practice, pharmacogenomics to the microbiome and companion diagnostics, this UBCMJ issue aims to explore the challenges and opportunities of this exciting field. We also aim to identify areas of health care that could benefit from these advances. Overall, this field of research is becoming increasingly relevant for medical students and physicians alike; the future of clinical practice rests upon providing high-quality patient-centred care, and medicine that is truly personalized will sit at the heart of it.

To encourage and recognize high quality writing, we will be presenting the **UBCMJ Distinguished Writing Award** (with a **$250** honorarium) to the strongest article submitted in the Fall 2017 and Spring 2018 issues.

What to submit:

- Academic Research
- Reviews
- Commentaries
- News & Letters
- Case and Elective Reports

We also accept submissions that do not fall into next issue's theme.

Submission Deadline: **March 11, 2017**
Submit at: **http://ubcmj.com/submissions/**

University of British Columbia Medical Journal

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