DMJ

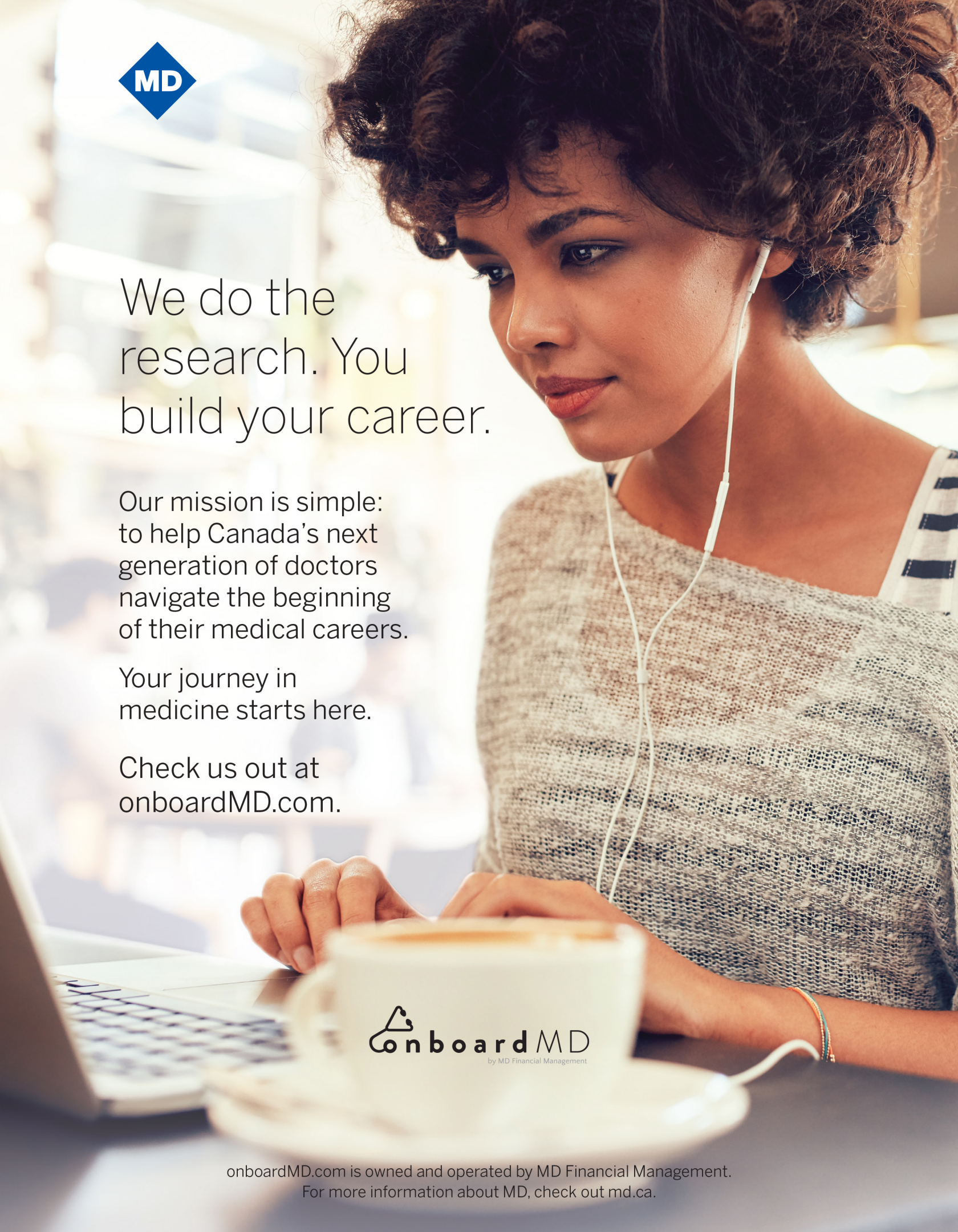
Dalhousie Medical Journal

Volume 45 | No. 2
Spring 2019

Opioid over-prescribing

Physician burnout

Pediatric autonomy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Credits
Cover image by Mike Wong

Layout design by Chansey Veinotte, Clara Long
Supported in part by the Dalhousie Medical Student Society

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ISNN 1488-9994
Publication Agreement number 4006-9552

Editor's message

Physician burnout: Current perspectives

Physician burnout, while likely existent since the profession of medicine itself, is a relatively new term. With the push for destigmatization of mental health, coupled with medicine's departure from a stoic worldview, physician burnout is now being recognized as a major problem facing our profession. Burnout can affect doctors at every stage of their training, from those in medical school to senior physicians. It carries major psychological burden, evidenced by suicide rates that are higher than the general population.[1] Additionally, physician burnout is associated with major medical errors, which can negatively impact patient outcomes.[2] Burnout is a multifactorial, complex problem, and the organizational and individual factors that contribute to its severity are not fully recognized. If these factors can be adequately identified, then preventative measures can be taken to reduce burnout risk while improving physician well-being.

As burnout becomes increasingly evident in residents, many, including mainstream media[3] and Resident Doctors of Canada[4] (RDC), have posited that prolonged working hours are a major part of the problem. Indeed, in 1984 an 18-year old female named Libby Zion was killed, as determined by a New York grand jury, by a constellation of poor decisions made by fatigued residents.[5] The message was clear: excessive working hours creates a situation in which patients' lives are at stake. In reaction, the Accreditation Council for Graduate Medical Education, a national governing body, enforced a limit on resident working hours to no more than 80 hours per week with no longer than 24 hours per shift, effectively bringing the USA in line with other developed countries (European Union and New Zealand) which have restrictions on resident work-hours.[6] To date, outside of Quebec (which has recently set a 72-hour per week limit with a 16-hour limit per shift), there is no national regulation surrounding resident working hours in Canada.

While there is ample evidence that work hour restrictions leads to better patient care, the effects of restricted work hours on physician burnout are less clear.[7,8] In a recent systematic review, quality-of-life and burnout were generally associated with long work hours in only a third of the studies examined, but not in others.[9] For example, in a recent study, restricted work hours (which caused increased average daily sleep) did not decrease feelings of burnout when measured in medical residents using a validated scale.[10] Strikingly, in one prospective cohort study of over 2000 medical residents in the US, stricter duty hours had no significant effect on hours slept, depressive symptoms, or overall well-being.[8] Together, this data suggests that while hours worked may contribute to some feelings of burnout amongst physicians, additional psychosocial factors play a major role. That said, there is certainly an argument to be made for duty hour restriction with respect to patient care, but it is clearly not an end-all solution for physician burnout.

Resilience, or the ability to recover from and resist the negative effects of stressful stimuli, is a major protective factor against the effects of depression.[11] Understanding that burnout can ultimately lead to depression and suicide, some have suggested that training physicians to be resilient may be an effective strategy. This includes training individual aspects of resilience such as positive coping and thinking strategies, building support systems, implementing physical activity, and self-care; as well as organizational and community factors such as teamwork, cohesion, a sense of belonging, and a positive work environment.[12] Indeed, physicians who engage in self-care and maintain positive outlooks on work and life felt the effects of burnout less than those who did not.[13] Some healthcare systems, recognizing the major burden associated with burnout, have implemented support programs for physicians suffering from burnout, wherein a physician self-identifies (or a colleague raises concern about) their burnout and is then paired with a mentor who acts as support.[12] Other systems have implemented programs that promote a culture of wellness (both physical and mental), self-reflection, teaching of resilience techniques, and compassion.[12] Overall, organizations have a responsibility to support their physicians when burnout occurs.

Nova Scotia is no stranger to physician burnout, and many of the above factors are at play. A recent survey conducted by Doctors Nova Scotia (DNS) showed that 50% of surveyed doctors have symptoms of burnout and 20% felt ineffective at their job.[14] These numbers are alarming, considering the current physician shortage the province faces which, in turn, puts higher strain on current practicing doctors and further contributes to burnout. Interestingly, the major contributor to burnout in the DNS survey was not lack of self-care but was rather mostly organizational. Thirty percent of physicians felt their autonomy was disrespected by government/health authorities, 45% felt they lacked autonomy in their work environment, and many had concerns regarding billing, uncompensated time, and excessive workload due to poor physician recruitment.[15] In an effort to ameliorate some of the effects of burnout, DNS has developed programs (the

Professional Support Program, available via the DNS website) and workshops to support physicians when needed.

The solution to reducing physician burnout, especially in Nova Scotia, is multifactorial and will require reform by a variety of stakeholders. That includes an evaluation of working hours of residents and other physicians, a push for individual training of resilience in medical curriculums and at the organizational level, and an implementation of adequate support programs in healthcare organizations. Most importantly, for Nova Scotian physicians, is improved communication and cooperation between government, physicians, and health authorities. Stakeholders should be reminded that our priorities lie with maximizing patient outcomes. With physician burnout so prevalent, it is challenging to continually provide our patients with the highest level of care. It is therefore in the best interest of all parties to try and address this problem.

Dan Vidovic
Editor-in-Chief

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Review

The opioid epidemic: How did we get here and where do we stand?

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Background

For the last 5000 years opioid medications derived from the opium poppy have been utilized by various cultures for their analgesic properties. Over the last 2000 years opioids have become a cornerstone in the management of moderate to severe pain. As the use of these medications has become more widespread, it has become apparent that their beneficial properties might be overshadowed by their potential downsides.[1]

Western, Arabian, and Chinese cultures have described cases of opioid addiction following opioid use dating back to the 16th century.[2] This frightening trend of opioid addiction subsequent to using opioids for their analgesic properties has persisted to the present day where it has reached epidemic-level proportions. As pharmaceutical companies became aware of this problem, they were quick in attempting to develop opioid medications that possessed the same analgesic properties but lacked addictive potential. Drugs such as meperidine, oxycodone, hydrocodone, methadone and oxycodone were all developed and originally marketed as opioid medications lacking addictive potential.[2]

Unfortunately, evidence has shown that each of these drugs possess a high addictive potential. During the 1980s, prescribing of opioid analgesics skyrocketed, in part due to this misinformed marketing.[3,4] At the heart of this prescribing surge were two articles: one by Porter and Jick[3] entitled "Addiction rare in patients treated with narcotics" and another by Portenoy and Foley[4] entitled "Chronic use of opioid analgesics in non-malignant pain: report of 38 cases". Both of these articles demonstrated the safety of opioids in treating acute and chronic pain while largely downplaying the dangers associated with opioid use, namely their abuse and lethal potential. Pharmaceutical companies frequently cited these papers, using them to convince physicians of the safety of opioid analgesics in treating patients' pain. The strategy worked – opioid sales increased dramatically. Further fuelling the opioid prescription surge was the awareness of pain as the "5th vital sign". This idea was first presented by Dr. James Campbell in 1995 and led to patients' pain being regularly evaluated, often by physicians with no experience in pain management.[5] Pain is often assessed using the Numeric Rating Scale (NRS) wherein patients rate their pain from 0 to 10 (0 = no pain; 10 = the worst possible pain). If non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were ineffective for patients with significant pain on the NRS, they would often be prescribed opioids to relieve their pain. Opioid prescriptions were often guided by both a lack of education surrounding pain management, but also the ease of writing a prescription when physicians had little time to spend with their patients. Prescriptions of opioids increased dramatically as physicians aimed to normalize their patients' 5th vital sign.[5] Unfortunately, this surge in opioid prescriptions also led to increases in opioid diversion, abuse, addiction, and frequently, overdose. Indeed, opioid overdose death rates increased 5-fold between 1980 and 2008 in the US.[2] Interestingly, this increased opioid prescribing rate did not lead to a reduction in patients' pain scores.[2]

Research has shown that opioid use is associated with immunosuppression, opioid-induced endocrinopathy, and paradoxical opioid-induced hyperalgesia.[6] Furthermore, there are a myriad of side effects associated with opioid use, including (but not limited to) sedation, constipation, delirium and respiratory depression. Opioid-induced respiratory depression - leading to hypoxemia and ultimately cardiorespiratory arrest - is the primary cause of mortality associated with their use and is potentiated by various pulmonary conditions and the combined use of other CNS depressants.[6] In light of more recent literature regarding the dangers of opioid use, the quantity of opioids dispensed in Canada (as measured by defined daily doses - DDDs) has declined from 238 million in 2012 to 226 million in 2016.[8] Of note, although the number of DDDs has decreased, the overall number of prescriptions has increased from 20.2 million in 2012 to 21.5 million in 2016. While there is no national data available prior to 2016, opioid-related deaths in Ontario have ballooned from 366 in 2003 to 865 in 2016. A similar trend is seen in Quebec, where deaths have escalated from 62 in 2005 to 133 in 2015.[7,8] Furthermore, the trend is moving east with Nova Scotia averaging 60 acute opioid toxicity deaths per year between 2011 and 2017 (Figure 1).[9] This would suggest that though the number of pills dispensed has decreased, the number of opioid prescriptions and opioid-related deaths have increased.

Opioid Use

Opioid prescriptions in the US have increased 4-fold since 1999, the most commonly prescribed medications

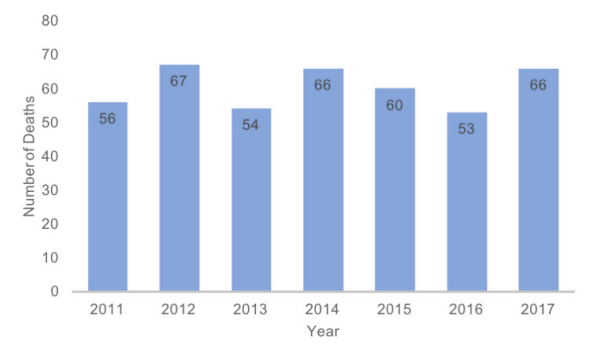

Figure 1: Number of opioid deaths in Nova Scotia between 2011 and 2017[9]

being oxycodone and hydrocodone. Notably, these are also the medications most commonly associated with opioid-related deaths.[6] It has been shown that following low-risk surgery, up to 80% of patients are prescribed opioids for analgesia; 80% of which are oxy- or hydrocodone.[6] As their pain dissipates, patients frequently keep their leftover medication instead of properly disposing of them.[6] This behaviour, coupled with opioid over-prescribing, has contributed to the observed increase in opioid diversion, abuse and addiction. Several risk factors for chronic opioid use following surgery in the opioid naïve patient have been identified. These include: male sex, age >50, preoperative use of benzodiazepines and/or antidepressants, history of depression, history of alcohol/drug use, low socioeconomic status, and preoperative pain.[6] Moreover, chronic opioid use does not only impact the patient. Leftover medications are often given to family or friends to treat their pain, laying the groundwork for a new cycle of misuse. A dramatic increase in opioid-related motor vehicle fatalities, from 0.1% of all motor vehicle fatalities in 1995 to 7.2% in 2015, demonstrates that opioid use can continue to affect lives outside of those related to the patient.[6,11]

The problem of opioid abuse recently reached a peak in 2014, when more individuals in the US died from drug overdoses than any other year on record and greater than 60% of these deaths involved opioids. As a result, the US Centers for Disease Control and Prevention released a compilation of 12 evidence-based guidelines for physicians prescribing opioid analgesics for chronic pain:[12]

Determining when to initiate or continue opioids

1. Opioids are not first-line therapy
2. Establish goals for pain relief and function
3. Discuss risks and benefits

Opioid selection, dosage, duration, follow-up, and discontinuation

4. Use immediate-release opioids when starting
5. Use the lowest effective dose
6. Prescribe short durations for acute pain
7. Evaluate benefits and harms frequently

Assessing risk and addressing harms

8. Use strategies to mitigate risk
9. Review Prescription Drug Monitoring Program (PDMP) data
10. Use urine drug testing
11. Avoid concurrent opioid and benzodiazepine prescribing
12. Offer treatment for opioid use disorder

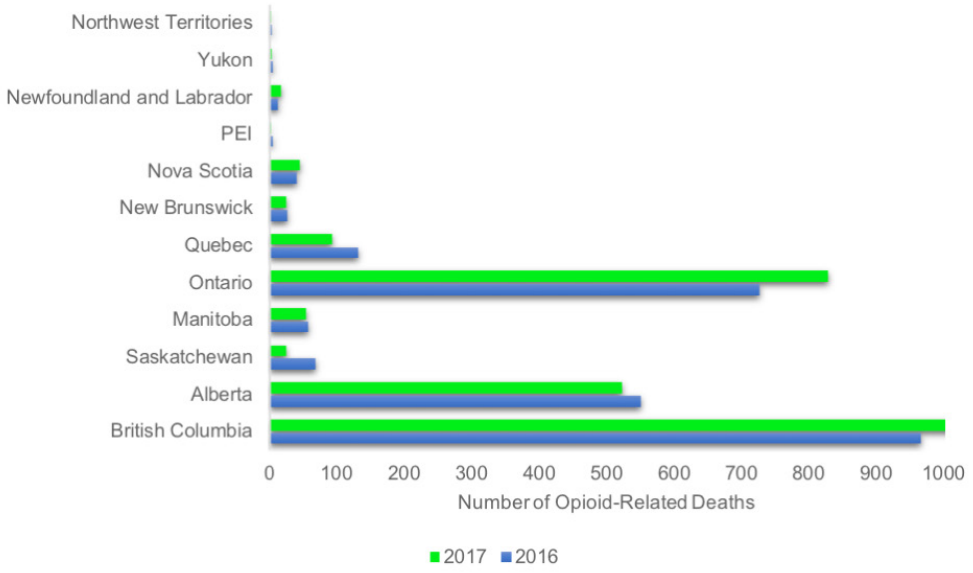

Figure 2: Number of opioid-relates deaths by province in 2016 and 2017[10]

As previously mentioned, opioid analgesia may often fail as an intervention for chronic pain despite increasing dosage. This is due in part to the complexity of the condition. Chronic pain can be altered by several comorbid factors including depression, anxiety, poor coping skills, personality, sleep, and concurrent substance use disorders.[13,14] The presence of chronic pain may exacerbate a patient's psychiatric, functional, and social difficulties, all of which can act to influence their opioid use. The importance of this cannot be understated as it demonstrates that chronic pain may best be treated using a multimodal approach in contrast to increasing opioid dosages.[13,14]

Addressing the Opioid Crisis

1) Use of Opioid Adjuvants and Alternatives

The use of non-opioid adjuvants has recently gained traction as an option to reduce perioperative opioid use. These include non-opioid adjuncts (acetaminophen and NSAIDs), nerve blocks and block additives, among others. Kumar et al. describe several non-opioid adjuvants, some of which are outlined below.[15] It should be noted that some opioid adjuvants also have significant abuse and diversion potential (most notably ketamine). Their use should be monitored accordingly:

1. Dexmedetomidine – an α2 adrenoreceptor agonist. Dexmedetomidine possesses central antinociceptive activity thought to be mediated through α2 stimulation in the dorsal horn. A 0.5-1 μg/kg bolus ± intraoperative infusion has been shown to decrease opioid consumption for 24 hours postoperatively, without a concurrent increase in patient pain scores.
2. Clonidine – also an α2 adrenoreceptor agonist. Clonidine is primarily used as an antihypertensive medication but has also been shown to reduce opioid consumption for 24 hours postoperatively.
3. Ketamine – an N-methyl-D-aspartate (NMDA) receptor antagonist that decreases nociceptive transmission. Low-dose intravenous ketamine following surgery has been shown to reduce opioid use by 40%
4. Dextromethorphan – also an NMDA receptor antagonist. Perioperative administration (40-120 mg IM or 30-200 mg oral) of dextromethorphan has been shown to decrease pain up to 24 hours following surgery and morphine use for up to 48 hours.
5. Duloxetine – an oral serotonin-norepinephrine reuptake inhibitor (SNRI). Duloxetine elicits its antinocioceptive effects by modulation of the descending inhibitory pain pathways. Several studied have demonstrated that its perioperative use can decrease opioid consumption following surgery for up to 48 hours, though it does not alter pain perception.
6. Lidocaine – when administered intravenously, a bolus of lidocaine (1-3 mg/kg) followed by an infusion (1-2 mg/kg/h) can lower pain scores for up to 24 hours following surgery and decrease perioperative opioid use. It is currently recommended as part of the Enhanced Recovery After Surgery (ERAS) intraoperative protocol, particularly when epidural analgesia is not used.

In addition to the use of non-opioid adjuvants, the use of nerve blocks with or without general anesthesia has been associated with decreased perioperative pain scores and opioid usage.[15,16] For example, continuous interscalene blocks have been shown to have a prolonged analgesic effect for up to 24-48 hours postoperatively, working to reduce opioid consumption. Additionally, patients undergoing hysterectomy who received an epidural reported lower postoperative opioid consumption and pain scores in comparison to those who underwent general anesthetic. Block additives, such as dexamethasone and clonidine, can work to increase the efficacy of nerve blocks by significantly increasing the duration of action of the block, helping to further reduce opioid consumption and patient pain scores.[15,16]

As mentioned above, chronic pain can be modulated by several comorbidities, including depression, smoking and anxiety.[13,14] For individuals with a history of these conditions, Hah et al suggest that these patients may benefit from preoperative and ongoing postoperative cognitive behavioural therapy (CBT) in order to help curtail the risk of opioid abuse and misuse.[6] Furthermore, Vetter et al suggests the implementation of a Transitional Pain Service (TPS), where applicable.[17] The TPS is a longitudinal program pioneered at Toronto General Hospital which focuses on at-risk and vulnerable surgical patients who are without adequate support for pain management. Participants in the program must meet the following criteria: a) history of chronic pain; b) previous or current psychological comorbidities; and c) be consuming large amounts of opioids either pre- or post-operatively. As such, the goal is to tackle the issues of chronic pain and opioid use pre- and post-operatively. Patients enrolled in TPS programs are treated with conventional pharmacotherapy, such as gabapentinoids and tricyclic antidepressants (TCAs), in addition to perioperative psychological and holistic treatments. Teams involved with TPS are large, multidisciplinary teams composed of an anesthesiologist/pain medicine specialist, internal medicine hospitalist, addiction medicine specialist,

pain psychologist, licensed social worker, and advanced practice registered nurse. The aim of TPS is to aid those patients who are at high risk of long term, excessive opioid consumption and in turn, limit opioid abuse, addiction, and diversion.[17]

2) Naloxone in Managing Acute Overdose

Now synonymous with opioid overdose, Naloxone (allyl-noroxymorphone) was first recognized in the early 1960s. Before then opioid overdose was treated with levallorphan, a compound that, itself, could cause respiratory depression at high doses. When allyl-noroxymorphone treatment was compared with levallorphan, it was found to be 2-6 times as potent and also did not cause respiratory depression or any other unpleasant side-effects even at high doses.[18] Further studies have demonstrated the risk of several side-effects, including pulmonary edema, seizures, arrhythmias and hypertensive crisis. It is difficult, however, to determine if these side-effects are caused by the administration of naloxone, the underlying disease processes, or other drugs that have been ingested or administered.[19,20] Overall naloxone is considered a safe and effective treatment for opioid overdose.[20]

Since then, naloxone (commonly sold in Canada under the trade name Narcan) has become a staple in the treatment of opioid overdose. Naloxone was first distributed to heroin users in 1995 in Germany and England,[21] with community opioid overdose prevention programs following soon after, rapidly becoming commonplace in North America and Europe.[22] These programs, aimed at teaching members of the community about recognizing and responding to opioid overdose, typically included a few core components: recognizing the signs of overdose, strategies to prevent overdose, risk factors for opioid overdose, appropriate response to opioid overdose, and how to administer naloxone in the event of an overdose.[22] These programs have been shown to increase bystander knowledge of prevention, risk factors and recognition of opioid overdose. Further, there is evidence that the use of these programs increases the bystander use of appropriate overdose strategies.[22] One study, performed in Massachusetts between 2006 and 2009, evaluated the correlation between implementation of their Overdose Education and Naloxone Distribution (OEND) programs and the rate of opioid related deaths from overdose. They found that regions implementing OEND programs were associated with lower rates of opioid related deaths from overdose when compared with regions with no OEND implementation.[23]

In many provinces in Canada, Naloxone kits are available free of charge to those at risk of an opioid overdose or those who may witness an overdose.[24-27] In Nova Scotia, and several other provinces, individuals must complete a brief training session prior to obtaining the kits, the content of which is akin to the aforementioned prevention programs.[24] Emergency departments across North America have also developed their own opioid overdose protocols and varying naloxone dosages, the details of which are beyond the scope of this article.[19] This demonstrates that life-saving methods that are used in emergency departments can also be employed in a similar way for overdoses that occur in the community.

Providing education and treatment for opioid overdose in the community is an important step in combating the sequelae of the opioid epidemic on the front lines. Reduction in fatal overdose rates in regions with access to overdose education and treatment methods has shown early promise. Though the rates of fatal overdoses have declined in these areas, the core of the opioid issue must be tackled from higher powers, including governmental bodies and the medical institution as a whole.

3) Current Strategies to Manage the Opioid Epidemic

In 2010, the National Pain Centre at McMaster University developed the original Canadian Guideline for Safe and Effective Use of Opioids for Non-Cancer Pain.[28] This guideline outlined several important recommendations for physicians to adhere to when prescribing opioid medication in order to help prevent adverse outcomes. Given more recent research surrounding opioid prescribing, an updated version of the guideline titled "The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain" was released by the National Pain Centre at McMaster University in 2017. The updated document outlines the following ten recommendations for opioid-prescribing physicians:[29]

1. Pain in patients with chronic non-cancer pain should be addressed by optimization of non-opioid pharmacotherapy and non-pharmacologic therapy in place of opioid therapy (strong recommendation).
2. Patients with chronic non-cancer pain, who have persistent problematic pain despite optimized non-opioid therapy, can be trialled on opioid therapy (weak recommendation).
3. Opioid therapy is advised against in patients with chronic non-cancer pain with an active substance use disorder (strong recommendation).
4. In patients with an active psychiatric disorder and chronic non-cancer pain, who have persistent problematic pain despite optimized non-opioid therapy, it is suggested that the psychiatric disorder be stabilized prior to trialling opioid therapy (weak recommendation).

5. In patients with chronic non-cancer pain with a history of substance use and persistent pain despite optimized non-opioid therapy, it is suggested that physicians continue non-opioid therapy rather than trialling opioid therapy (weak recommendation)
6. In patients with chronic non-cancer pain beginning opioid therapy, it is suggested that prescribed doses remain less than 90 mg morphine equivalents per day (strong recommendation).
7. In patients with chronic non-cancer pain beginning opioid therapy, it is suggested that prescribed doses remain less than 50 mg morphine equivalents per day (weak recommendation).
8. In patients with chronic non-cancer pain currently using opioid therapy, it is suggested that physicians rotate to other opioids if pain persists rather than keeping the opioid the same (weak recommendation).
9. In patients with chronic non-cancer pain currently using ≥ 90 mg morphine equivalents daily, it is suggested that opioids be tapered to lowest effective dose, potentially including discontinuation (weak recommendation).
10. In patients with chronic non-cancer pain currently using opioids and experiencing challenges in tapering, a formal multidisciplinary program is recommended (strong recommendation).

Since the publication of these guidelines in the Canadian Medical Association Journal in May of 2017, they have been adopted by the majority of medical colleges across Canada; in British Columbia, Alberta, Ontario, and Nova Scotia.[30-33] In addition to these guidelines, many provinces are taking further steps to address the opioid crisis. Examples include the implementation of harm reduction programs in Alberta, development and implementation of Prescription Monitoring Programs in New Brunswick and Newfoundland and Labrador, and the development of further evidence-based standards regarding opioid prescribing in Ontario.[34-37] The hope is that with the advent of these guidelines, physicians will have a framework for decisions surrounding opioid prescribing.[29] Further, implementation will ultimately lead to decreases in opioid abuse, diversion and dependence.

In 2017, the Association of Faculties of Medicine of Canada (AFMC) concluded that pain, addiction to pain medication and medical management of pain were not adequately addressed in either the undergraduate or postgraduate Canadian medical curricula.[38] Following this observation, AFMC has begun the process of developing and implementing a curriculum addressing these deficiencies. Key aspects of the curriculum would include: the diagnosis and assessment of pain; treatment of pain; safe prescribing, monitoring and discontinuation of pain medication, focusing on opioids; adverse effects of opioids; and prevention of misuse and medication diversion, among others.[38] The current proposal is to develop and implement the curriculum from early 2019 through to mid-2020 at selected medical schools, with evaluation of the curriculum being completed by the end of 2020.[39]

Since the AFMC's 2017 report was released, their 2018 update praised several Canadian medical schools for developing courses or curricula around these topics. Most notable were a Year-4 clerkship course in pain management and the opioid crisis at UBC, a course on safe prescribing practices for several medications at Memorial University and an integrated program at Dalhousie University for Residents in PGME.[40] Education of the next wave of physicians is paramount to ensure they enter the workforce with a thorough understanding of the benefits and dangers of opioids. It is expected that the knowledge of the impact opioids can have on a patient's quality of life will shape prescribing practices of the next generation of physicians from the outset.

Summary

For the last 2000 years, opioid use has been integral in the management of moderate to severe pain. Though efficacious in treating pain, we are currently in the midst of an opioid epidemic as we are learning that these medications have significant side effects. They possess a high addiction potential and research has shown that opioid use may also be associated with immunosuppression, opioid-induced endocrinopathy, and paradoxical opioid-induced hyperalgesia. Furthermore, the side effects associated with opioid use include sedation, constipation, delirium, respiratory depression and death. Despite the known issues surrounding these medications, they are still being prescribed at an alarming rate, leading to a year-over-year increase in opioid-related hospitalizations and mortality. In light of this, the CDC recently released a set of guidelines for physicians to adhere to when prescribing opioids in hopes of curbing the current epidemic. Indeed, while the guidelines are helpful, physicians and patients should be made aware of risks, potential alternatives to opioids in treating pain and options to mitigate opioid use. These include the use of opioid adjuvants (e.g. Dextromethorphan), the use of nerve blocks as an alternative to general anesthesia, and at-risk patient involvement in programs such as TPS. Further, governmental bodies and medical curricula alike are aiming to combat the opioid epidemic from the lens of the initial prescriber. While we may be in

the midst of an opioid epidemic, the accumulation of changes such as these may begin to slowly, but surely, help to curtail our overreliance on opioids.

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Review

The role of direct oral anticoagulants (DOACs) in the treatment of heparin-induced thrombocytopenia (HIT): An evidence-based literature review

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Abstract

Heparin-induced thrombocytopenia (HIT) poses a risk of death secondary to thrombotic complications. Treatment options are limited for patients with poor IV access, as contemporary options are restricted to parenteral agents before switching to oral vitamin k antagonists. A literature review was conducted to examine the effectiveness of direct oral anticoagulants (DOACs) in the primary treatment of HIT. High quality evidence is scarce surrounding the use of DOACs for this indication, while past reviews have not critically appraised the evidence. Additionally, the most recent study from 2017 investigating the use of DOACs for this indication has not been reported in past literature reviews. The Cochrane Library, Embase, PubMed, Google Scholar and ClinicalTrials.gov were searched to identify and critically appraise the best available evidence. Salient literature demonstrates that DOACs are effective at raising platelet count to baseline after seven days, on average. Thrombosis and major bleeding are rarely observed when DOACs are used as primary therapy. While large scale studies are needed, patients with HIT that have poor IV access may benefit from the ease of administration, rapid onset of action and lack of routine monitoring associated with DOAC therapy.

Introduction

Used for deep vein thrombosis (DVT) prophylaxis, unfractionated (UFH) and low-molecular weight heparins (LMWH) may cause heparin-induced thrombocytopenia (HIT), an adverse drug reaction.[1] HIT is immune-mediated, occurring when heparin-induced antibodies interact with platelet factor 4 (PF4).[1] Activated platelets mediate the release of prothrombotic microparticles and induce platelet consumption, resulting in the development of thrombosis and eventually, thrombocytopenia.[2] Defined as a 30-50% decrease in platelet count from baseline, thrombocytopenia ensues five to ten days after exposure.[1] Reduction in platelet count >50% from baseline, a nadir of $\geq 20 \times 10^9$/L and skin necrosis at the heparin injection site increase the likelihood of HIT according to the 4Ts scoring tool.[1] Complications of HIT include limb amputations as well as DVT and pulmonary embolism (PE).[1] HIT is associated with a 5-10% mortality rate secondary to thrombotic complications.[1]

Treatment options for HIT include fondaparinux (Arixtra), lepirudin (Refludan), bivalirudin (Angiomax), danaparoid (Orgaran) and argatroban (Argatroban); the latter two are approved by Health Canada for this indication.[1] Fondaparinux's off-label use stems from observational data and is associated with a thrombosis rate of 16%.[3] Lepirudin is currently not available in Canada and is given IV, similarly to bivalirudin.[1] There is a 25% thrombotic event rate when treated with danaparoid or argatroban.[3] These parenteral anticoagulants must be transitioned to vitamin K antagonists (VKAs) following platelet recovery, increasing cost and risk for warfarin-induced microthrombosis.[4] The high rate of thrombotic events, difficulty of administration and the need for routine monitoring with warfarin (Coumadin) necessitate alternative treatment options.[4]

Anecdotal reports suggest DOACs are effective in treating HIT after treatment failure with conventional agents.[5] DOACs do not interact with PF4, lending them an advantage over danaparoid and fondaparinux, which may cross-react with HIT antibodies.[1,7,8] Oral administration, rapid onset of action, ease of use and the lack of routine monitoring make DOACs an attractive treatment option for HIT including patients with poor IV access.[8]

Clinical Question

In a patient with poor IV access, would DOACs be a safe and effective option for primary treatment of HIT to reduce the risk of thrombosis and bleeding?

Search Strategy

The Cochrane Library, Embase, PubMed and Google Scholar were searched between November 12th, 2017 to February 13th, 2018. Keywords included "thrombocytopenia", "heparin-induced thrombocytopenia", "HIT", "anticoagulants", "novel oral anticoagulants", "NOACs", "direct oral anticoagulants", "DOACs", "rivaroxaban", "dabigatran", "apixaban", and "edoxaban" (Figure 1). This generated 5214 articles, which were limited by publication type (meta-analyses, systematic and literature reviews, randomized controlled trials, clinical practice guidelines, and journal articles), year

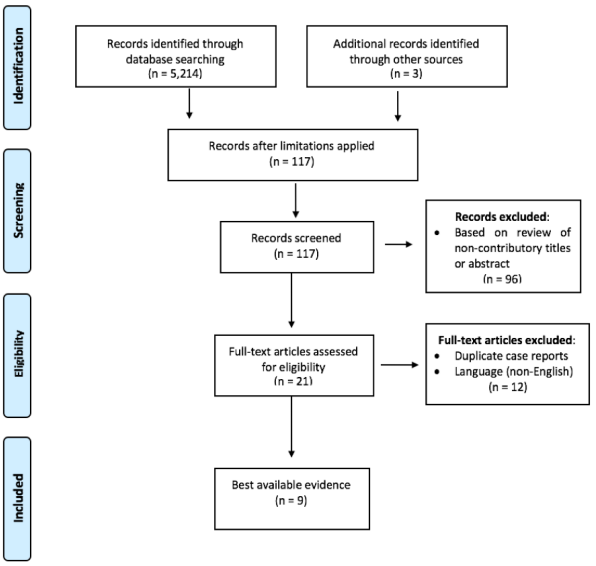

Figure 1: Search Strategy and Selection Process

of publication (last 10 years), and language (English). Articles were screened by reviewing titles and abstracts to ensure they examined the treatment of HIT with DOACs. As such, patients switching from parenteral HIT therapy, those with comorbidities such as cancer or end-stage renal disease and specific patient populations dissimilar to the population for our clinical question such as pregnancy, nephropathy and post cardiac surgery, were excluded to mitigate potential contributors to negative confounding bias. A total of nine articles were relevant to our clinical question. The data reported in these studies are summarized in two articles, which were deemed to be the best available evidence. This included a combined retrospective cohort study[4] and systematic review[4,11] as well as a separate retrospective cohort study.[9] ClinicalTrials.gov was searched on May 2nd, 2018 to identify studies that are ongoing, unpublished or withdrawn and yielded no additional articles.

Results

DOACs have been shown to be effective for patients with HIT, although few trials evaluate their use as treatment for this indication. Of these studies, most investigate the use of DOACs as secondary treatment for HIT following the use of conventional agents; however, studies that examine the use of DOACs as primary treatment for HIT have demonstrated positive results. The best available evidence is summarized in a combined retrospective cohort study[4] and systematic review,[4,12] while the most recent evidence stems from a cohort study conducted in 2017.[9]

A retrospective cohort study identified 16 patients in four hospitals in Hamilton, Ontario with a 4Ts score >4 points and a positive test for HIT antibodies.[4] Patients were stratified by initial treatment with a DOAC or with a non-DOAC before bridging to a DOAC. Only 8 patients received a DOAC as primary treatment. Doses varied from 15-30mg of rivaroxaban daily, with a median treatment duration of 3 months. Patients were evaluated after 30 days to assess for thromboembolism, major bleeding and time to platelet recovery. Seven of the eight patients receiving rivaroxaban as primary treatment were thrombocytopenic before initiation of treatment, with a median platelet count of 56,000/μL. No thrombotic events or major bleeding were observed. The average time to platelet recovery was 7.3 days.[4]

The systematic review assessed patients with a 4Ts score ≥4 with HIT antibody detection.[4,12] Patients were included with a 4Ts score of ≥6 if antibody testing was unreported. The 30-day thrombotic event rate and major bleeding rate were evaluated. While doses varied, 69 patients received rivaroxaban, dabigatran or apixaban. Rivaroxaban was assigned to 46 patients with a median platelet count of 73,000/μL; of these patients, only 25 received primary treatment with a DOAC. The frequency of new, progressive or recurrent thrombosis was 2.2% (95% CI, 0.4%-11.3%). One episode of thrombosis was observed, resolving upon removal of a central venous catheter and continued treatment with rivaroxaban. No major bleeding was observed. Apixaban was assigned to 12 patients, while 11 patients received dabigatran, for a total of 23 patients with a median platelet count of 58,000/μL. One patient had a thrombotic event, while none experienced major bleeding.[4,12] Since this combined paper was published, new research has been conducted.

A retrospective cohort study conducted in 2017 assessed 12 patients with 4Ts scores ≥4 that tested positive for HIT antibodies.[9] If serotonin release assays yielded a negative test result, patients were excluded from analysis. Primary outcomes included thromboembolism, gangrene or amputation due to critical limb ischemia during hospitalization. Nine patients received apixaban while three patients received rivaroxaban for an average of 9.33 days (ranging from one to 32 days) at varying doses. Eleven patients continued DOAC therapy post-discharge. At baseline, five patients had HIT-associated thrombosis. Of the 12 patients, seven were given argatroban before receiving a DOAC irrespective of thrombosis status. No patients experienced thrombosis or major bleeding and the mean time to platelet recovery was 7.42 days.[9]

Discussion

High quality evidence supporting DOACs in the treatment of HIT is scarce. Nevertheless, the retrospective cohort study from Hamilton, Ontario showed that the use of rivaroxaban as primary treatment

for HIT is promising.[4] Explicit criteria for the diagnosis of HIT and platelet count recovery improved internal validity. Patients were evaluated after three months, allowing sufficient time to determine the efficacy and short-term safety of DOACs. However, internal validity was compromised as fondaparinux may also cause HIT[1], but the causative agent of HIT was never stated.[4] Only five patients had a high probability of HIT while two were classified as intermediate probability.[4] If HIT was not present and an incorrect diagnosis was reached, efficacy may have been overestimated. Heterogeneity between patient characteristics, varying doses and unreported methods of thrombosis measurement further mitigated the legitimacy of the results. As patients ranged from 54-94 years of age, older patients may have been more sensitive to adverse effects such as bleeding. Initial indications for heparin treatment varied. External validity was reduced by the small, specific subgroup of patients in Hamilton, Canada and by the variation in initial indications for heparin treatment.

The systematic review demonstrated encouraging results for the usage of rivaroxaban, dabigatran and apixaban for this indication. Search strategy, inclusion and exclusion criteria and assessment of outcomes were stated a priori, ameliorating the quality of the study design. Both English and non-English articles were searched, limiting publication bias, while a clinical diagnosis of HIT was explicitly defined. However, in patients without HIT antibody confirmation, it was not explained why other causes of thrombocytopenia were unlikely. Potential inclusion of cases of thrombocytopenia unassociated with heparin limits internal validity, as these patients may have had more favourable outcomes.[4,12]

Studies included in the systematic review did not adequately report patient characteristics including medical history and concurrent drug therapy. Sufficient details surrounding methods and the assessment of outcomes in these studies were limited. It was not stated how studies were assessed for quality, minimizing internal validity of the pooled results as patients may have been heterogeneous, while doses and duration of therapy were not standardized. Of the 46 patients treated with rivaroxaban, 21 patients received a parenteral anticoagulant beforehand, making it more difficult to extrapolate the results. Physicians may also have been hesitant to prescribe DOACs as long-term risks for patients under this indication have yet to be established. Thus, channeling may have been present, as patients prescribed DOACs may have had a more favorable prognosis, increasing the likelihood of achieving positive results.

Data from the most recent study published in 2017 affirms the positive results from the existing evidence, as platelets were observed to recover after a median 7.42 days with no major bleeding or thrombosis.[9] Strengths of the study include that diagnosis of HIT, major bleeding, time to platelet recovery, inclusion criteria and outcomes were explicitly defined. The usage of serotonin release assay (SRA) boosts the quality of the study, as SRA is virtually diagnostic for HIT.[10] However, SRA testing was not performed on each patient, increasing the risk of selection bias, as patients may have had more favorable outcomes if they were actually SRA negative. Short-term follow-up, inclusion of patients with HIT-related thrombosis, lack of individualized patient results, use of DOACs as secondary treatment, varying doses and small sample size minimize internal and external validity. Patient comorbidities were not reported while long-term outcomes were not assessed.

Conclusion

There is a lack of high-quality evidence investigating the use of DOACs in the treatment of HIT. There are currently no published meta-analyses or randomized controlled trials addressing this topic, while the only systematic review is small. Although scarce, evidence supporting the use of DOACs for the primary treatment of HIT is promising; especially with rivaroxaban. With demonstrable efficacy with respect to recovery of platelet count, DOACs have the potential to become viable treatment options for HIT. In comparison to standard options for HIT treatment, DOACs were reported to have a lower incidence rate of thrombotic events.[4,9]

The best available evidence maintained the reputable safety profile of DOACs as there was no bleeding reported when used to treat HIT.[4,9,12] Despite their relatively high cost, medication adherence is facilitated by their ease of administration, lack of monitoring requirements and possibility of oral dosing. Earlier hospital discharge is possible as they can be used post-discharge, reducing the risk and expense of switching to VKAs.[4]

For patients with poor IV access, treatment options for HIT are limited. Fondaparinux has been used more frequently but has a high thrombotic rate, may interact with PF4 and is more difficult to administer.[1] Evidence supporting the use of fondaparinux in the treatment of HIT is weak.[4] Of the DOACs, rivaroxaban has the most research supporting its use to treat HIT at a dose of 15mg twice daily for four weeks.[4] Studies evaluating the use of edoxaban for this indication have not been conducted. Further advancements should target randomized controlled trials with large sample sizes, stratifying patients to each of the DOACs as well as

standard treatment options with long-term follow-up. Comparative safety and efficacy data will cement the role of DOACs in the treatment of HIT.

Acknowledgements

We would like to acknowledge Emma Murray for her efforts in helping us with this literature review.

Conflict of Interest Statement

There are no conflicts of interest by any author pertaining to this submission.

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Opinion

Decision-making through the lens of a pediatric cancer case

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Abstract

It is crucial to obtain a competent individual's informed consent in any medical process, including cancer treatments. However, when it comes to incompetent children, it seems to be favourable, but not necessary, to obtain their assent in medical practice.[1] This paper considers Christine Harrison's example of Samantha, an eleven-year-old girl that was treated for osteosarcoma in her left arm. Samantha had previously been treated by amputation and a course of chemotherapy. This cancer later metastasized to her lungs, decreasing her chances of remission with aggressive treatment to 20%. Although she wanted to refuse treatment, she was deemed incompetent to make decisions about her cancer care, and her parents adamantly wanted her to continue treatment.[7] This paper considers physicians' moral obligations in pediatric cancer cases such as Samantha's. I will define assent, the principles of autonomy, beneficence, and competence as it pertains to children. I consider arguments of two opposing views–a child's rights view that argues in favour of Samantha's decision, and a paternalistic view that opposes her. After reviewing the bioethical literature on the risks and benefits of children's decision making in health care, I argue that Samantha's wishes to stop treatment ought to be respected. Throughout the paper, I will use the bioethical principles of respect for autonomy and beneficence to defend my position. Finally, I address potential objections my position may face and conclude.

It is crucial to obtain a competent individual's informed consent in any medical process, including cancer treatment. However, when it comes to incompetent children it seems to be only favourable - not necessary - to obtain their assent in medical practice.[1] I will consider Christine Harrison's example of Samantha, an eleven-year-old girl that was treated for osteosarcoma in her left arm.[7] Samantha had previously been treated by amputation and a course of chemotherapy. Although she was cancer free for 18 months, she was self-conscious about her prosthetic and had to give up her cat for fear of infection. This cancer later metastasized to her lungs, decreasing her chances of remission with aggressive treatment to 20%. Although she wanted to refuse treatment, she was deemed incompetent to make decisions about her cancer care, and her parents adamantly wanted her to continue treatment.[7] Although Samantha's parents legally have the final say in her cancer care, what are physicians' moral obligations in pediatric cancer cases such as Samantha's? After reviewing the literature on the risks and benefits of children's decision-making in health care, I will argue that Samantha's wishes to stop treatment should be respected. This paper will be composed of three sections. In the first, I define the moral status of children, basic bioethical terms, as well as two opposing views that pertain to decision-making in pediatric cases. In the second, I apply these definitions to the bioethical principles of respect for autonomy and beneficence to defend my position. In the third, I consider objections that my position faces and conclude.

Section I: Definitions and Assumptions

First, this paper will assume that the moral status of children is as described by Brennan and Noggle for whom children are of equal moral status as their parents and are not owned by the parent. That is not to say that they have the same rights as their parents, as having certain rights entails that one has a certain role. For example, children cannot drive because that right comes with a responsibility that children cannot fulfill due to their incompetence.[3] Parents, on the other hand, are stewards. They have a responsibility to exercise their children's rights and refrain from violating these rights, as well as to promote the best interests of the child.[3] However, parents are often put in situations where they must balance the interests of their other children and the interests of the entire family. I will touch on family interests in the following section and argue that promoting Samantha's best interests does entail respecting her wishes to stop aggressive treatment.

Next, there are four bioethical principles to which health practitioners adhere when administering care: respect for autonomy, beneficence, non-maleficence, and justice.[7] When addressing issues in pediatric cases, usually the principles of autonomy and beneficence are explored by health practitioners.[7,9] The principle of respect for autonomy states that competent individuals have the right to make decisions for themselves, even if these decisions are not in their health-related interests; the principle of beneficence urges health practitioners to act in the best interest of their patients.[7] I will use these concepts throughout this paper to demonstrate that Samantha's wishes ought to be respected.

In order to adhere to the principle of respect for autonomy, informed consent is sought by health practitioners in clinical settings. Informed consent allows health practitioners to perform procedures that otherwise would not be acceptable, and it has five components: competence, disclosure, understanding, voluntariness, and token consent.[8] If any of these five components are not met, the consent is not valid. For the purposes of this discussion, competence is the most relevant component of informed consent. Competence in particular is task and time-dependent and may be met if one can give recognizable reasons for one's decisions.[7] There are different stages of competence when it comes to minors. Infants and very young children are assumed to lack competence. Then, minors enter into the stage in which they develop competence. Competence, in this stage, is a continuum that needs to be assessed individually, based both on the nature of the procedure and the current stage of cognitive development of the patient. Being in this stage, Samantha may be able to participate to an extent in decisions regarding her care, but not fully. Finally, once minors reach the age of majority (typically around eighteen) they are assumed to have developed full competence.[7] In pediatric settings, children who are incompetent or are developing competence can give their assent to a procedure.[9] Assent retains the disclosure and voluntariness requirements of consent, but dispenses with the requirements of competence and understanding which would be expected from an adult.[8] Although the bioethical literature recommends that a child assent to a procedure, a child's decision to dissent to life-saving treatment, such as that of Samantha, can be overruled.[9]

To conclude the first section, I will outline two opposing views on decision-making in pediatric cases. The first is a paternalistic view, according to which parents ought to make health-related decisions for their children.[9] If we were to apply the paternalistic view to Samantha's case, Samantha's parents ought to make the final decision on her care, regardless of her dissent. The second view I will call a "children's rights" view and is popular within the bioethical literature.[3] The children's rights view is an umbrella term for a number of different perspectives that seek to increase the role that children have in their own treatments. Thus, one should recognize that there are many ways in which children's rights views can be interpreted. Some children's rights views may border on the paternalistic view, while others assign the same rights to children as adults. However, children's rights differ from adult rights in the ways outlined by Brennan and Noggle – having a right is dependent on having a role that allows you to exercise said right.[3] Thus, for the purposes of this paper, the children's rights view is nuanced, and argues for stronger respect for a child's consent, but not complete adult rights. Furthermore, in clinical practice, children can dissent to their medical treatments and are part of the decision-making process for their care. However, their dissent may be overruled by their parents or medical staff in life-threatening cases.[9] When applying the children's rights view to Samantha's case, one must analyze various factors before choosing to accept her dissent. Both the paternalistic and children's rights views appeal to arguments that touch on increasing children's autonomy and the best interest standard, which is the western standard of care when it comes to pediatric cases.[5]

Section II: Analysis

The following paragraphs will pertain to the principle of respect for autonomy. In pediatric oncology cases such as Samantha's, it is not sufficient to simply state that accepting her decision allows for the principle of respect for autonomy to be achieved. Various arguments pertaining to decision-making in pediatric cases appeal to the principle of respect for autonomy as a reason (but not the sole reason) children should (or should not) be free to make a medically-related decision.

First, as Samantha is a minor, she is not deemed legally competent to make a life-or-death medical decision related to her osteosarcoma.[7] Her parents are thus required to practice Samantha's autonomy for her.[3] Supporters of the paternalist view may argue that there is no objective test to assess competence for every single individual, thus we may not truly know that Samantha is competent to make decisions in a pediatric oncology context.[9] However, a 2006 study by Alderson et al. demonstrated that children with diabetes were able to understand and reach an acceptable level of competence when it came to their illness, and were able to make their informed medical decisions in this context.[1] Furthermore, as described in section I, competence can be assessed using the recognizable reasons standards. Although this standard is not completely objective, Samantha has given recognizable reasons to discontinue care–– the treatment is aggressive, the prognosis is poor, and she wants to die a peaceful death. Given that competence is context dependent and Samantha has undergone cancer treatments in the past, she may understand how the aggressive cancer treatments make her feel – something her parents are unable to do. As explained in section I, this allows Samantha to be awarded certain rights to make this decision, as she has taken on the

role of a cancer patient, but does not allow her to make any decision she pleases.[3] This role allows Samantha to understand what it is like to undergo treatment, how this treatment affects her body, her mental state as well as her social context. Therefore, it is reasonable to believe that Samantha has capacity in this case to make a decision regarding her care.

Those that agree with the paternalistic view may argue that Samantha's parents should have the final say in her care because it is important that Samantha's long-term autonomy is respected, not simply her present-day feelings.[9] Samantha's decision does little to respect her long-term autonomy, as her decision will ultimately lead to her death. But we can also assess one's long-term autonomy by looking to retroactive consent.[3] An example of retroactive consent as it pertains to cancer care can be given by examining the case of Brian Fies's mother in his book "Mom's Cancer". After looking back at her aggressive treatment to cure her brain cancer, Brian's mother stated that she would not have consented had she known her chances of survival were low and the toll the radiation would take on her body.[6] Assuming Samantha survives to adulthood, would she give her retroactive consent to the procedure? It is plausible for an adult Samantha to question her parents' decision to continue with her cancer care given the inconvenience of aggressive treatment and the high chance that she will die an arguably unpleasant death. Given the aggressive nature of treatment in cancer cases, it is understandable for adults to refuse life-saving treatment, and instead, choose to live out the rest of their days on their terms. Thus, it may be that in Samantha's case her decision to discontinue treatment does not harm her long-term autonomy.

The following paragraphs will pertain to the principle of beneficence. The best interest standard stems from the principle of beneficence and is the standard western society uses to medically treat children.[7] This standard is often consequentialist, and usually opts for life-saving treatments as saving one's life is arguably in their best interest.[4] In some cases, if parents do not consent to life-saving treatments for their children, physicians have the right to intervene in the name of the child's best interest.[4] There are several ethical issues surrounding the best interest standard. The first is that often children are deemed competent if they make the "right" choice and incompetent if they choose to stop treatment, like Samantha.[1] Furthermore, this standard can be ambiguous, as it is very difficult to determine what is in one's objective best interests in these tough medical contexts, and it is often left to physicians to make this decision.[2] Samantha pursuing aggressive cancer treatment may not necessarily be in her overall best interests. There are several reasons that support this statement.

First, De Vries et al. conducted a study in a pediatric oncology setting about what parents and physicians assume to be the best interest of children in this context. During the early stages of diagnosis and treatment, parents deemed survival to be in the child's best interest and were willing to do whatever physicians recommended. However, after the initial shock of the cancer diagnoses subsided, parents and children felt that what is in one's best interests are values outside of medical context like leading a good life, having a sense of control, and maintaining their identities – either through religion or other ways.[5]

The paternalist view on decision-making in healthcare might argue that we trust parents to make decisions that are in their child's best interests in general – for example, which schools they attend, and what food they eat.[4] Therefore, Samantha's parents are probably the best equipped to know what is in her health interests as well. However, the child's rights view may reply that not only are parents making decisions that benefit Samantha but a decision that benefits their family as a whole, and this may override Samantha's personal interests.[4] In some cases, it is important to take into account general familial interests when dealing with patients, and it is obvious that Samantha's passing is going to change her family's dynamic and will be extremely difficult on her parents and any siblings she may have. However, Samantha's chances of remission are very low, and it is possible she is going to die with or without treatment. Thus, it may not be in this family's best interests to spend their last few moments with Samantha in a setting where their daughter is clearly uncomfortable and fighting with them.

Finally, Samantha expressed feelings of self-consciousness about her prosthetic, as well as being upset about giving up her cat "Snowy". She had shown extreme discomfort throughout her treatment and even struggled violently, which made the medical staff reluctant to keep administering treatment. Samantha stated that so much had been taken away from her and she was upset that her parents wanted her to give up even more.[7] Samantha's case can be mirrored through a case presented by Kunin. A.P. was a 12-year-old with an osteosarcoma in his arm, and eventually, after several aggressive treatments that did not seem to prove effective, he expressed the desire to spend more time

with his family and friends and leave the hospital.[8] It is important to note that if Samantha were to pursue aggressive treatment, there would be a twenty percent chance of remission. In A.P.'s case, however, there was no chance of remission thus exposing him to more pain, and toxicity from aggressive treatments might border on child abuse.[8] Although there is this difference between the two cases, Samantha's chances of remission are arguably low. Perhaps switching to a palliative care setting to die an arguably better death than she would have at the hospital is best.

Section III: Objections and Conclusion

The following paragraphs will address potential objections one could raise against my position, and offers replies that further justify Samantha's decision to end life-saving treatment.

One may argue that there is a morally significant difference between allowing an elderly person to make a life-ending medical decision and allowing Samantha-although potentially competent, to do the same. This is due to the number of life years lost. For example, if an elderly person such as Brian Fies's mother decides to end an aggressive, possibly futile treatment, what is lost is a few years of life. However, in Samantha's case, although the chances of success in her treatment are low, if she does survive she will gain an entire lifetime.

In reply, while it is true that should Samantha's treatment work she will gain more life years than an elderly person in her position, this argument is not consistent with current medical practice. Ethically, clinicians allow competent young adults and teenagers to make life-ending medical decisions in order to respect their autonomy and non-health related values. There are many life years lost in these contexts as well, but these decisions are justified not based on life years lost or gained.

One may object that if Samantha is able to make a life or death decision regarding her health, then she should also be able to make other decisions about her life that traditionally adults make.[9] For example, Samantha could be a student at an elementary school, and as most students in elementary school, she would rather be on summer vacation or sleeping in than in the classroom. Given the nature of the arguments in section II, since Samantha goes to school every day, she knows better than her parents about her school environment. Thus, if one day Samantha decides to drop out of elementary school, she should be able to do so. Through this comparison, if one accepts that Samantha can make life or death decisions, one must also accept that Samantha should be able to drop out of school.

In reply, there is a morally significant difference between Samantha's decisions regarding her cancer treatment and her decisions regarding school. The first is, as I have demonstrated above, discontinuing aggressive cancer treatment and allowing Samantha to live out the rest of her days with her family and friends may be in her best interests and might not harm her future autonomy. Dropping out of school, however, is arguably not in her best interests, and can potentially harm her overall autonomy because her opportunities to make choices will be reduced if she does not get an education. To highlight this point further using the retroactive consent argument described in section II, most adults would not give their retroactive consent to drop out of elementary school. Furthermore, competence is context dependent as described above. Although Samantha can make a life or death decision regarding her case, that does not mean that Samantha can make a decision surrounding her education. There are two reasons for this. The first is that Samantha has given recognizable reasons for her wanting to discontinue her care as argued in section II. The second is that there are little to no recognizable reasons for wanting to drop out of elementary school that outweigh the objective benefits of an education. Thus, Samantha can make a life or death decision regarding her cancer care but still is unable to make the decision to drop out of elementary school.

In conclusion, Samantha's wishes to stop treatment for her osteosarcoma should be respected. After considering arguments from both the paternalistic and child's rights views pertaining to autonomy and best interest, I have concluded that physicians have a moral obligation towards Samantha and her decision. Although Samantha is a minor, her autonomy should be respected as she may be competent to make this decision given her context, and her future autonomy might not be harmed in doing so. The best interest standard commonly used in pediatric medicine has flaws that are disadvantageous to Samantha. Samantha has other values aside from her health-related values that contribute to her best interests, and these should be respected by the health practitioners. Samantha's parents eventually decided to respect her wishes to die after consulting with the team of health practitioners as well as an ethics board. They took Samantha home where she was given a new cat and died peacefully.[7]

Acknowledgements

I would like to acknowledge Dr. Lynette Reid from Dalhousie University's Department of Bioethics, Dr. Kirsten Borgerson from Dalhousie University's Department of Philosophy, and Cameron Yetman for their contributions to this paper.

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Research

Male catheter insertion simulation using a low-fidelity 3D-printed model in undergraduate medical learners

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Abstract

Urinary catheter insertion is one of the most widely performed procedures in a clinical setting. Inexperienced catheterizations constitute a high percentage of urethral trauma in hospital settings, with as high as 75% of comorbidities related to inaccurate insertion. Simulation training can help learners feel more confident, shorten the learning curve, and provide a safe learning environment for novices to make, and learn from, mistakes. Three dimensional (3D)-printed simulation models are as effective as commercially available models for novice learners, and have the benefits of being inexpensive, anatomically correct, portable and can be easily modified and rapidly produced as needed. A 3D-printed male urinary catheter insertion simulation model, designed by MUNMed 3D, was offered to Memorial University medical students as part of pre-clerkship procedural training. Fourteen students were provided with a checklist for the procedure and the 3D-printed urinary catheter insertion simulator, and following the simulation, were asked to complete a 5-point Likert survey on their experience. The average self-reported skill before using the model was 1.29 (out of 5), which increased to 3.21 (out of 5). All 14 respondents selected either "agree" or "strongly agree" for the following four survey items: the simulation was an accurate anatomical representation, they would prefer learning on this simulation model before performing this procedure, they would recommend the model to other learners, and they found this model beneficial overall. Simulation training with a 3D-printed urinary catheter insertion simulator allows trainees the opportunity to become confident and familiarize themselves with the procedure before performing it on a real patient.

Introduction

Urinary catheter insertion is a widely-performed procedure in the hospital setting for patients who lack bladder function or require a fluid status assessment.[1,2] To perform this medical procedure, a hollow tube is inserted through the urethra and into the bladder; once inside the bladder, the end of the catheter is inflated to prevent spontaneous removal. The inserted catheter allows for passage of urine out of the body, or for urine measurement when considering the intake and outflow of fluids. Although widely performed in the hospital setting by various healthcare practitioners, this procedure is expected to be performed by Canadian undergraduate medical students as they rotate through the clinical setting.[3] As with any invasive procedure, there are risks and complications associated with catheter insertion. Improper catheterization technique can result in urethral trauma and may contribute to catheter-related urinary tract infections.[3,4] In some centres, up to 75% of reported urethral trauma following a catheterization is caused by learners, highlighting the need for early and efficient training in this procedure.[5] Traumatic catheter insertion is recognized as a major cause of iatrogenic urethral strictures, resulting in obstructive or irritative urinary symptoms that have a profound impact on patients' quality of life.[6]

With healthcare focusing on patient safety and successful outcomes, a need has been identified to achieve these goals in the area of the urinary catheter insertion procedure. As mentioned, urinary catheter insertion is a mandatory skill for medical students in their clinical years of undergraduate training. The students should complete the procedure under direct supervision of their preceptors to ensure accurate completion of the procedural steps in the correct order, with sterility preserved. To prepare for procedural training and the clinical clerkship experience, many medical schools provide a "pre-clerkship" training course that offers simulation for commonly performed medical procedures. Despite being one of the most prevalent procedures[1], lack of experience with urinary catheter insertion is an ongoing concern for undergraduate learners at the pre-clerkship level. This learning gap can be fulfilled using three-dimensional (3D) printed simulation models, allowing students to practice the steps of the procedure and familiarize themselves with this technique. This simulation training can assist learners in feeling more confident when performing urinary catheterization, reducing the potential for complications that can occur as a result of inexperience.[7] Simulation training allows trainees to make mistakes without the implications of litigiousness

or causing harm, which offers a strong learning experience for skills development.[8] Specific to urinary catheter insertion, simulation training has been shown to increase user confidence which offers a significant advantage when first facing an insertion in an evaluated clinical setting.[7]

Three-dimensional printing is becoming more prevalent throughout the medical fields due to technological advancements and decreased production costs.[9] In simulation-based medical education (SBME), 3D printing has several distinct advantages. In healthcare centres that have access to 3D printing technology, a design can be printed as a point-of-care simulation without the need for expensive commercial grade models; this would be especially beneficial in rural and remote areas. Indeed, 3D printed simulators are less expensive than most simulation kits commercially available, but can be just as effective for the acquisition of skills in novice learners.[10] Due to the ability to print anatomically correct models, 3D printing models are being widely incorporated into simulation training in multiple surgical fields and other specialties.[11,12] This is also ideally suited for medical learners to familiarize themselves with the steps of a procedure without risk of patient adverse events.

The aim of this project was to help fill an educational gap identified in the undergraduate medical school curriculum for urinary catheter insertion. A low-cost, 3D printed simulation model was developed to assist undergraduate learners in the acquisition of confidence and procedural skill knowledge prior to clerkship rounds in a hospital setting. This article describes the development of the male urinary catheter insertion simulator, the feedback obtained from novices on the design, and concludes by presenting a framework for future developments of the 3D printed urinary catheter simulation model.

Methodology

The male urinary catheter insertion simulation model was designed under guidance of a staff urologist (Figure 1). The model was 3D printed using an Ultimaker 3, with 20% infill and 0.2 mm layer height. The base, water reservoir (urinary bladder) and mounting structures were printed using red polylactic acid (PLA) and the external genitals were cast in Smooth-On 00-30 silicone. The urethral component was printed with polyurethane thermoplastic elastomer (TPE) in durometer 80A. The overall cost of the model was approximately $35, with the silicone external genitals costing $30 and the rest of the print materials being less than $5. This estimate does not include the initial design time.

The urinary catheter insertion simulation was carried out by preclerkship students during procedural training, where the model was set up in a separate unsupervised area of the simulation lab for participants to practice with on their own time. The study was described to participants, who consented to the study by completing the survey. A checklist was provided to the participants to guide the participants through the correct steps of urinary catheter insertion. The checklist used was incorporated from a validated Delphi survey and contribution from a staff urologist.[13] Participants were provided with a catheter insertion kit and given up to ten minutes to practice the steps of the procedure using the model. Following the use of the model, a survey was provided to the participants to complete. Questions were asked using a 5-point Likert scale and were intended to assess how the learner's confidence and experience changed with use of the model, the anatomical accuracy of the model and their overall impression of the model. Participants were presented with a series of statements related to these objectives and were asked to select on a 5-point bipolar Likert scale their level of agreement with the statement (strongly disagree to strongly agree).

This project is a quality improvement initiative in the procedural training of urinary catheter insertion, and whether the implementation of a low-cost simulation would be beneficial to learners. As such, questions were designed to generate qualitative information about the

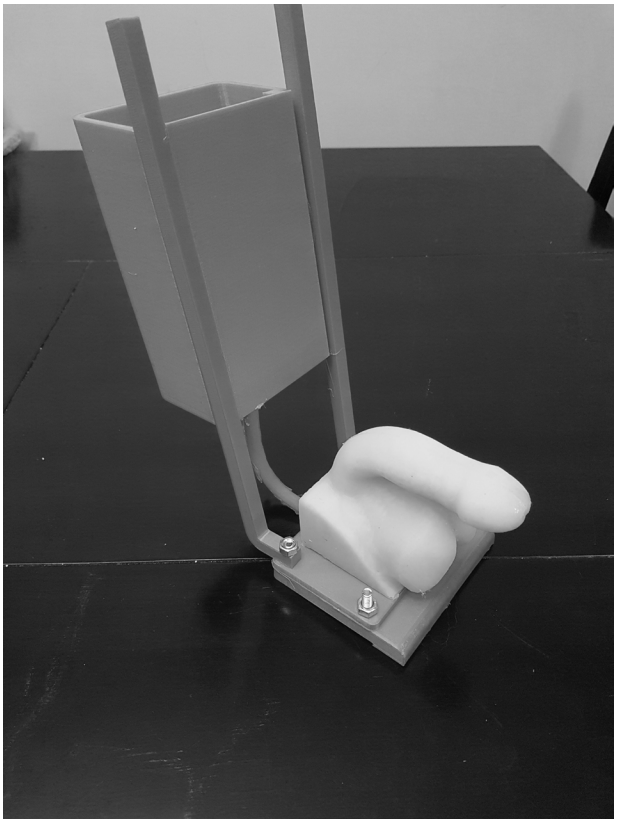

Figure 1: 3D-Printed Urinary Catheter Insertion Model

Table 1: Post-simulation survey results from preclerkship trainees.

Survey Component	1	2	3	4	5	Mean
1. What was the level of your skill before using the simulation?	11	2	1	0	0	**1.29**
2. What was the level of your skill after using the simulation?	0	1	9	4	0	**3.21**
3. The catheter insertion model felt realistic.	0	0	7	3	4	**3.79**
4. This simulation was an accurate representation of the relevant anatomy.	0	0	0	11	3	**4.21**
5. When using this model, all steps of urinary catheter insertion can be carried out.	0	1	3	5	5	**4.00**
6. I would prefer learning on this simulation model before performing insertion on a real patient.	0	0	0	4	10	**4.71**
7. I feel more confident in performing catheter insertion.	0	0	2	8	4	**4.14**
8. I would recommend this simulation to undergraduate medical learners.	0	0	0	5	9	**4.64**
9. Overall, I found this simulation beneficial.	0	0	0	8	6	**4.43**

model itself and generate a solution for the learning gap identified in the project design. This project was considered a product evaluation and improvement project, and therefore exempt from ethics review.

Results

Results of the survey are presented in Table 1.

Surveys were completed by 14 participants who practiced catheter insertion on the 3D-printed model. The average self-reported skill before using the model was 1.29 (out of 5), which increased to 3.21 (out of 5) after using the model (Table 1). Of the 14 participants, 14 (100%) chose either "agree" or "strongly agree" for the following four statements: the simulation was an accurate anatomical representation, they would prefer learning on this simulation model before performing this procedure, they would recommend this model to other learners, and they found this model beneficial overall. In addition, 10 respondents (71.4%) would prefer using this model before performing the procedure on an actual patient.

Discussion

The 3D catheterization model was designed to create a meaningful learning experience as an alternative to existing, commercially available models, with fidelity maximized in the confines of ease and low cost of modifications and replications. Additionally, the 3D printed model incorporates a few unique design features not available in urinary catheter insertion simulators on the market today. The silicone penis is easily manipulated, allowing for straightening of the urethra during insertion of catheter. As the catheter is advanced into the bladder, it passes through a valve that mimics the sphincter muscle, keeping fluid in the bladder without leaking out. Once the sphincter is breached, water will return through the catheter. The end of the catheter can be visualized upon entering the bladder, allowing the user to ensure that the catheter is in the correct position before inflating the balloon. This feature allows the learner to appreciate the drawback of the inflated balloon against the bladder neck, and ensure the catheter is securely in the correct position.

Collectively, these features provide additional sources of visual feedback, which can be beneficial for novice medical learners.[14] For example, a randomized controlled trial by Zhong et al. compared the use of a transparent urinary tract simulator to a traditional simulator for the teaching of urological skills.[15] After learning on the transparent simulator, the experimental group scored significantly higher on procedural skills testing than the control group. The ability to visualize the anatomy of the urinary tract and appreciate exactly where the catheter is in relation to important structures is helpful in preventing trauma that results from inflating the balloon while still in the urethra. To that end, one of the major advantages of the 3D simulator is that the learner can see the catheter enter the bladder and inflate the balloon correctly. As a result of the study by Zhong et al and feedback from this iteration of the 3D catheterization model, a future direction would be incorporating transparent materials in the design of the model.

Using this knowledge, the urinary catheter model we designed will undergo revision and a secondary prototype model will be created. A more rigorous iterative validation process will occur, with a cohort of undergraduate medical and nursing students evaluating the product in tandem with existing high-fidelity models. Undergraduate nursing learners, who will ultimately insert a large majority of catheters in the clinical setting, may also benefit from this model for procedural training. As the simulation model has yet to be formally evaluated by expert users of the procedure (i.e. urologists), its implementation as a learning tool is uncertain; but this early research suggests that a low-fidelity 3D-printed urinary catheter insertion simulation model has the potential to be an effective addition in learning this procedure.

As this iteration of catheter model was intended as a prototype to better inform the identified learning need, the next step in enhancing the simulation experience would be the incorporation of modular elements in the model design. The base of the model would act

as a static element, allowing for the replacement of individual design pieces such as the urethra or external genitalia. This way, a female model could be designed by swapping out the genitalia and urethra, but keeping the bladder and base, allowing for a quick switch between models. Training for difficult catheterizations would be accomplished by replacing the urethral anatomy to include a stricture or an enlarged prostate, then assessing how a learner would manage this scenario. These modifications can be shared between sites with access to 3D-printing materials, allowing for point-of-care simulation in remote areas without access to more expensive models.

One limitation of this study is the subjective self-assessment of a learner's increased skill in this procedure. This study isn't intended to comment on an objective increase in procedural skill from using this model, but rather as a correlate for increased user confidence, a subjective measure that can result in decreased patient and user anxiety. As many students have never performed a catheter insertion, it is difficult for them to comment on the anatomical accuracy of the model. Also, as one of the future settings for this model may be in nursing education, this study used a cohort of medical students, limiting the applicability of the results obtained.

Conclusion

This project represents an attempt to ameliorate a learning gap in the preclerkship curriculum of undergraduate medical learners, where a significant portion of respondents indicated that they would feel more comfortable and confident with additional training (including simulated training) in urinary catheter insertion. This procedure can be a stressful experience for both patients and professionals, and increasing user confidence can go a long way towards decreasing patient anxiety. With medical learners being implicated in a significant portion of catheterization related injuries, simulation training offers the advantage of practicing with the ability to make mistakes in a structured setting without the potential for adverse patient events.

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Humanities

From expressionless to impressionist: Exploring the link between neurological disease and artistic style in painters

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Abstract

This paper discusses the relationship between various types of neurological disease and stylistic changes in painters. By first outlining the hypothesized neuroanatomical bases of creativity, the discussion then relates localized brain damage to various stylistic changes in painters and previously non-artists. It also explores artistic style in the context of more global neurological damage, such as dementias and neurotransmitter imbalances. The literature suggests that focal neurological insults (such as strokes or head injuries) may more often lead to focal deficits in painters, such as the loss of visuospatial ability or partial hemineglect. More widespread neurological damage may be associated with more global stylistic changes; for example, dopamine replacement therapy for Parkinson's disease has been shown to produce a more impressionist painting style in numerous recorded artists. In several case studies, brain damage actually led to the emergence of de novo artistic ability. While these changes in artistic style may not be rigidly predictable based on the limited literature available, this paper demonstrates that both artists and non-artists may experience significant changes in artistic style after neurological disease. Patient narratives also suggest that painting may serve as an empowering personal coping and communication strategy, aiding patients in navigating their complex illnesses.

Introduction

Despite the breadth of artistic variety in the humanities, few sub-forms are as widely studied as the visual arts. In fact, painting is an artform so tempting that even our Neanderthal ancestors produced animal drawings – at times complex and extensive – on their cave walls. It is now widely hypothesized that the artistic abilities of humans evolved as a mode of communication, allowing us to relate to one another and consequently create more tight-knit communities for a greater survival benefit.[1]

In more recent centuries, our societies have focused thoroughly on the concept of style in individual artists. Because the increasing complexity of artistic style is temporally correlated with an increasing complexity of the human neural framework, it is of particular interest to study painters' styles in the context of neurological ailments. It may come as a surprise to some that numerous famous painters were known to have neurological diseases which greatly influenced their work. Among them are Vincent van Gogh (psychosis), Georgio de Chirico (migraine/epilepsy), Lovis Corinth (stroke), Georges Braque (head injury), and Guillaume Apollinaire (head injury).[2,3] This paper explores the potentially causal link between neurological disease and subsequent changes in artistic style.

It should be mentioned that, while the link between neurological insult and style change has been studied, and in some instances may be considered causal, there may be other factors at play which influence this correlational relationship. One is the reality that many artists' styles naturally evolve over time, sometimes slightly, but oftentimes substantially. Usually, however, this evolution in style is gradual and signifies the maturation of the artist over time.[3] Therefore, for the sake of exploring the hypothesis that neurological disease profoundly influences artistic style, we will closely examine some recorded cases of artists who exhibited sudden and profound stylistic changes (or even de novo artistic talent) in direct correlation to an identifiable neurological event. This will be achieved by discussing artists who suffer both localized neurological damage (e.g. a head injury or a stroke) and more widespread neurological change (e.g. dementia subtypes and neurotransmitter imbalances).

Neural Structures Associated With Creativity

Before discussing individual cases, it may be of some benefit to first discuss the various neurological structures that have been studied in relation to artistic style and creativity. While traditional doctrines postulate that the right hemisphere is the seat of artistic ability, research in recent decades has largely debunked this rather simplified view of artistic ability being a lateralized trait.[4] Many different areas of the brain have been identified as important contributors to the creative process. Lefebvre and colleagues noted that creativity in some birds was strongly associated with a more well-developed hyperstriatum and neostriatum (two regions found in avian brains).[5] In non-human primates, they found that the striatum (normally associated

with motor and reward systems) and the neocortex (normally associated with spatial reasoning, cognition, and sensory perception) are implicated.[5] These areas in particular have grown significantly throughout the evolutionary development of humans,[1,6,7] thereby establishing a temporal relationship between an increase in brain size and an increase in complexity of artistic style. Van Essen and colleagues used MRI technology to compare human to non-human brains and deduced that a larger left Sylvian fissure (the sulcus separating frontal, parietal, and temporal lobes), a larger right dorsomedial prefrontal region (the area housing our "sense of self"), and a larger right angular gyrus (normally responsible for number processing, language function, and spatial reasoning) may be key players in creativity.[6]

There are also interesting examples of brain structures which, if injured, may lead to the amplification of artistic ability. Shamay-Tsoory et al. determined (with a respectable sample size of 40 subjects) that anatomical lesions to the left posterior parietal cortex (responsible for spatial reasoning and motor movement planning) and posterior temporal cortex (associated with the ability to imagine another person's spatial perception) were associated with an increase in creativity.[8] In fact, the larger the lesion, the greater the effect. Meanwhile, lesions to the right medial prefrontal cortex (responsible for decision making) were associated with a decrease in creativity.[8] With these, and many other structures, implicated as "hotspots" for the creative process, creativity likely is not housed in a single hemisphere but relies on a complex interplay of various neural structures.[9]

These findings may beg the question of whether artistic ability is something that can be "created" as a result of damage to the brain. Many case studies and reviews have addressed this particular question. In an extensive review paper published in 2014, Zaidel presents a list of case studies that discuss the emergence of de novo creativity in people who began producing art only after brain injury.[1,10-16] However, instead of deducing that tissue injury leads to artistic "enlightenment," Zaidel came to a much more temperate conclusion: "there is a deep survival motivation to communicate through art when the communicative channel of language fails following brain damage." In other words, art is a way for patients to adapt to their new disability by creating a new mode of communication.[1]

Artistic Style and Localized Brain Insult

Patient cases that discuss artistic style in the context of a very localized brain injury (such as stroke or trauma) may give us insight into how the disruption of a discrete subset of neurons may affect a person's artistic ability. In a letter published in The Lancet, Miller and colleagues described three cases of enhanced artistic ability in patients suffering from a subtype of frontotemporal dementia, a type of neurocognitive disorder in which the anterior temporal area degenerates while the frontal lobes are mostly unaffected. This letter outlined that damage to neuronal systems in the anterior temporal lobe (responsible for inhibiting the posterior visual cortex) produced a profound sensory experience in patients. This consisted of intense visual memories and unfiltered visual perceptions of their surroundings, leading them to paint uninhibitedly.[17] This is one of several studies that propose a "disinhibition hypothesis," or the idea that, with certain inhibitory neural networks disrupted, the lack of available "brakes" now allows for the enhanced functioning of otherwise suppressed pathways (some of these studies will be discussed later). Bogousslavsky, another researcher in the field, supported this hypothesis with his own observations, writing that "[t]he capacity to 'disinhibit' […] repressed, controlled, mental processes is illustrated by the attempt of numerous artists to achieve a 'low arousal' state, which may allow the emergence of more 'spontaneous' expressions."[3]

Another fascinating case couples these observations with an instance of hemispatial neglect. A patient published as "The Painter From Sinaloa" underwent the removal of a central neurocytoma that resulted in the severing of right thalamo-parietal connections. The painter – previously producing full works of well-balanced canvases – now began to involuntarily neglect shapes in the left side of his paintings.[18] Astonishingly, instead of neglecting the entire left canvas as one might expect, he continued to paint contours and colours in the left half, but began to neglect elements like perspective and shapes. This resulted in works such as a green, hilly landscape throughout, but texturing elements like grass, flowers, and trees were restricted to the right half.[18]

There are two cases of famous artists who experienced a profound change in their artistic style after brain injury. Both Guillaume Apollinaire and Georges Braque sustained head injuries during WWI. Apollinaire, previously a poet, began to produce paintings in vivid watercolour while Braque, previously known for his cubist painting style, began to soften his sharp cubist abstractions and used more vivid colours.[3]

Another interesting question is whether artistic style changes may conform to laterality, i.e. whether brain injury in a certain hemisphere may translate into predictable changes to the artist's canvas. This question can be best answered by Italian neurologist Anna Mazzucchi whose research group studied various famous artists' pre- and post-stroke works and drew

conclusions based on the laterality of the insult.[19] This paper will outline four of her famous case studies.

Initially, let us discuss left-hemisphere strokes. The first example is that of Zlatyu Boyadjiev, a Bulgarian painter. Before his stroke, his works depicted semi-realist Bulgarian village scenes, often large crowds gathered around a fire. After the insult, his work became much more simplistic and impressionist with a strong decrease in perspective mastery.[19] Afro Basaldella, an Italian artist, is another example of a painter whose art became remarkably simplified after not just one, but two left-hemisphere strokes. His use of colour, previously realistic, became "opaque and simplified."[19]

Artists suffering from right-sided lesions exhibited different style changes. One example is that of Lovis Corinth, a German artist. His premorbid style reflected a robust adherence to realism: the subjects of his paintings, usually portraits, were conventional and realistic. After two right-hemisphere strokes, Mazzuchi et al. described his style as exhibiting "quick painting strokes, […], flat and rather elementary with hardly any tridimensionality."[19] His hemineglect became especially obvious in later years, with his paintings showing strong imbalances between the right and left sides.[19] The second example in this category is Otto Dix, another German painter. Originally also adherent to the naturalistic and academic painting style, he experienced profound challenges in coordinating volumes and space after his right-hemisphere stroke. His art also became entirely bidimensional with very basic colour schemes.[19]

While these are only four cases of the study's original six, Mazzucchi et al. were able to draw substantial conclusions. They found that painters with left-hemisphere lesions began to struggle with properly depicting perspective and often resorted to using repetitive geometric elements. Right-hemisphere lesions led to deficiencies in distance and depth, and the resulting visuospatial neglect often yielded imbalances in the left half of the canvas. Both groups regressed to the use of simpler, less realistic colours. Interestingly, the authors also found that the works of painters with left-sided strokes tended to improve over time, while those with right-sided strokes tended to improve very little, if at all.[19]

In summary, artists who suffered a discrete neurological insult generally experienced discrete artistic changes, such as neglect, visuospatial deficiencies, or regression to simpler colours. These changes may even be partially predictable based on which hemisphere is affected. Next, let us examine artists who suffered more widespread neurological damage.

Artistic Style and Widespread Brain Insult

In cases where brain damage is not neatly encased by penumbra and instead extends to large areas of the brain, we may observe different stylistic changes. Consider, for example, cases of neurocognitive disorders (dementias). It has been shown that persons with frontotemporal dementia and Alzheimer's disease remain active, creative artists through the course of their disease.[20-22] One particularly interesting case describes a woman with frontotemporal dementia whose style evolved with the progression of her disease. Originally trained in watercolour and Chinese brush painting, the progression of her condition was associated with an increasing tendency to paint large figures in bright colours, especially red, purple, and turquoise.[23] The author describes her last couple of pieces as intensely impressionistic with less detail, but more colour and more poignant emotional overtones.[23] There are also instances of de novo creativity in these patients.[20,24-27] Most of these cases are explained by authors' deference to the disinhibition hypothesis, relating the atrophy of inhibitory cortical pathways (a common feature of frontotemporal dementia) to a less restrained brain. However, this tends to be the exception rather than the norm, with most of the evidence showing that non-artists who become demented actually have lower creativity and artistic behaviour.[28] One possible explanation that marries these two observations is that of the "latent artist," meaning that the atrophy of inhibitory cortical pathways acts as a "release" of pre-existing artistic potential, rather than the de novo creation of it.[1]

Another way to look at more widespread neurological change is through neurotransmitters. The most predictable relation between neurotransmitters and artistic style is seen in dopamine. Parkinson's disease (PD), a movement disorder featuring tremors and postural instability due to insufficient striatal dopamine activity, is usually medicated with dopamine replacement therapy (DRT) via agents like levodopa. Multiple documented cases (discussed in subsequent paragraphs) have shown an increase in artistic output upon starting dopamine replacement. It has been argued that increased artistic productivity is not necessarily a unique side effect, as it is in line with other common side effects of DRT (such as an increase in impulsivity and gambling behaviours).[29] However, a study conducted by Canesi and colleagues suggested that de novo artistic ability after dopaminergic therapy in PD patients was not necessarily associated with impulsivity or impulse control disorders.[30] Therefore, increased artistic ability or productivity need not be seen as a reliable warning sign for impending impulsive behaviour.

While increased artistic productivity post-DRT initiation has been a relatively common observation by researchers,[31,32] style changes are starting to emerge as a Parkinsonian phenomenon.[33] More specifically, PD patients change their painting style post-DRT to one that is more impressionist (hence the title of this paper, "From Expressionless to Impressionist"). The emergence of this "Parkinson's Personality" has been the focus of many research groups. In a keynote address titled "Tremor: A biography of Parkinson's disease from the shaking palsy to the neurobiology of compulsion," prominent medical historian Dorothy Porter detailed a collection of paintings that became increasingly more impressionist in style after the artists began DRT.[34] This same trend was reported by Johanne Vermette, a former family physician and now painter living with PD. In a 2001 exhibition at the McGill Centre for Studies in Aging, she featured her art among that of seven other painters with PD. She has observed definite changes in her painting style since her diagnosis: "The new style is less precise but more vibrant. I have a need to express myself more. I let myself go, sometimes painting with enraged fingers."[35] Vermette also describes increased artistic productivity as a side effect of her DRT, often allowing her to paint late into the night.[35]

Porter's work also explores how these patients experience their change in artistic personality. In an extensive essay published in 2016, she tackles the question of how Parkinson's patients navigate this often rather sudden paradigm shift.[36] One example is that of Gwendoline Spurll, a hematologist at McGill University. Diagnosed with PD in 2005, she published a personal reflection on not only the changes of the meaning of her art after her diagnosis, but also how she perceives her own illness. "I do know that there are only two times when I forget about the Parkinson disease: when I am solving a difficult clinical case, and when I am painting," she writes. "It [painting] induces a flow state, and removes from my consciousness the constant knowledge of my physical limitation. It is like a meditation. It is my Zen."[38]

As a point of interest, there are various other artistic domains in which PD has been known to cause stylistic deviations. Schrag and Trimble reported on a PD patient who, upon starting DRT, began to write poetry de novo, eventually going on to win a prize for his work.[38] Another formidable example is that of Alan Babbitt, a photographer with PD who used a mechanical manifestation of his condition to his stylistic advantage. In order to compensate for the tremor he developed, he invented an entirely new style he termed "tremor-enhanced photography."[39] "When you first learn photography, they tell you over and over about crispness, about keeping the camera steady with a tripod," Babbitt writes. "One evening in Las Vegas, where I was alone with a digital camera, I just started shooting. I was able to see right away what I got. Blurs. Streaks. And then people started reacting to it, liking it."[39] His current artwork features brightly coloured cityscapes, lights, and abstract objects, often on black backgrounds to create sharp contrasts. He continued to name various of his portfolios after his condition, choosing names like "Shake me out to the Ball Game" or "Movement Disorder."[39]

Conclusion

Ultimately, neurological disease has the potential to produce significant changes in painting behaviour. Based on the studies available, it is possible that more localized brain injury (like strokes and head trauma) may lead to more focal changes in painting style. These include changes in visuospatial ability, colour choice, and the spatial distribution of objects. In more widespread neurological changes (like neurocognitive disorders or neurotransmitter imbalances), we see that changes more often reflect a global style change to one that is more daring and vibrant. The most predictable example of this phenomenon is reflected in the "Parkinson's Personality," an observation that the initiation of DRT often leads to a style that is more impressionist.

Acknowledgments

I would like to acknowledge Dr. Dorothy Porter for her intensely thought-provoking keynote lecture at the 2018 Canadian Society for the History of Medicine Annual Meeting. This talk served as the initial catalyst for my literature survey on the intersection of art and neurological disease, one of my most rewarding and curiosity-driven research endeavours to date.

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Humanities

Little hospital on the South Common: A history of the Victoria General Hospital

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Part of the Queen Elizabeth II Health Sciences Centre, the Victoria General is a tertiary care hospital in Halifax. It is a major referral centre for oncological care in the Atlantic provinces, is home to a Multi-Organ Transplant Program, and is host to a wide array of specialized medical and surgical services. The hospital has been at the forefront of medical education in Halifax since its inception, and has provided clinical instruction for numerous other health professions including: nursing, occupational therapy, respiratory therapy, radiological technology, and pharmacy.

This article summarizes the history of the Victoria General Hospital, which has served Halifax for one and a half centuries. During this time, it underwent a dramatic transformation from a last resort for the needy to a venerable modern academic hospital, while contending with political interference and perennial funding concerns. Though its zenith has passed, and its physical edifices have been ravaged by time, the Victoria General Hospital now drifts into its closing years having left a lasting impact on the health of Atlantic Canadians.

A Public Hospital for Halifax

While Halifax had military and privately-funded hospitals at times since the early days of European settlement, the city lacked a public hospital through most of the nineteenth century.[1,2] The affluent could hire personal nurses and physicians for care within their own homes, while less well-heeled citizens had few options aside from their own close relations.[3] In this era, public health was practically non-existent as a priority. The moneyed had little desire to extend care to the poor, particularly when social mores attributed disease to immoral behaviour. Nor were infant and child mortality likely a major consideration, since this population did not engage in useful work. The city's nearest approximation of a public hospital was likely the Poor House, a crowded facility simultaneously acting as a prison, an orphanage, a lunatic asylum, a workhouse for the jobless, and a shelter for the homeless.[3,4]

Starting in 1832, Halifax physicians unsuccessfully lobbied the City Council and the House of Assembly on multiple occasions for the founding of a public hospital and medical school.[4] 1844 brought some hope for this cause when mayor Hugh Bell offered to donate his entire year's salary (£300) toward establishment of a public charity, yet bureaucracy and difficulties soliciting additional donations ended the project.[5,6] In 1854, news of a severe cholera outbreak in Saint John, New Brunswick may have finally motivated government action.[2] The next year, City Council passed a resolution to issue bonds up to £5000 toward erection of a City Hospital.[7] It would be located on the South Common, bounded by Tower Road, South Street, and Morris Street (Figure 1). This site was a popular place for shooting game birds, and enjoyed a small degree of seclusion that was potentially beneficial for containment of epidemics.[8]

A two-level, red brick building with two short wings to the north and south, the City Hospital was large enough to accommodate 35 patients, and its construction was completed in 1859.[5,7,8] Unfortunately, it was plagued by a variety of challenges from the outset. As it focused on the care of "infirm and diseased indigents," the hospital was regarded with casual contempt by Halifax's middle and upper classes.[5] The local medical community also argued about how to organize the hospital's medical staff, and whether physicians should somehow be paid for treating the hospital's impoverished clientele. The physical infrastructure was deemed inadequate, with the water and gas supply, stoves, and drainage all subject to bitter criticism.[6] Lastly, unsatisfactory management was coupled with public antagonism toward paying for the facility on an ongoing basis.[5-7] The City Hospital was quickly shuttered, and opened only on an irregular, intermittent basis during its early years.

Thanks to years of persistent advocacy by Halifax's Health Officer, Dr. Charles Tupper, as well as a cholera outbreak in 1866, an arrangement was made for the provincial government to split the cost of running the hospital with the city of Halifax.[1,5-7] Oversight of the hospital was then placed under the Board of Public Charities, which also managed the Poor House and the Nova Scotia Hospital in Dartmouth.[7,9] The newly-re-christened Provincial and City Hospital once again opened its doors in 1867, receiving its first patient on April 15th.

Dr. James Venables, a recent Harvard graduate, served as the first house surgeon and medical superintendent, living in the hospital while working on-duty twenty-four hours a day, assisted by a rotating cadre of visiting staff.[2,5,9] Initially, nursing at the Provincial and City Hospital was rudimentary, even for the time.[8] Despite efforts to recruit mature women with reasonable and kindly sensibilities, domestic service was still considered a preferable occupation; thus, many

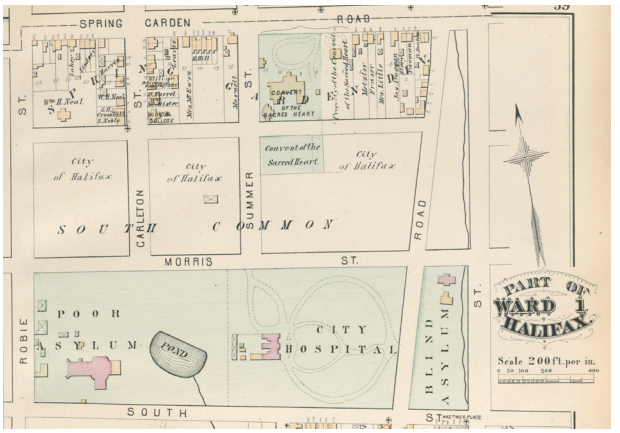

Figure 1: Location of the City Hospital. The stretch of Morris Street depicted here is now part of University Avenue. From the City Atlas of Halifax, Nova Scotia. 1878.[87] Courtesy of Nova Scotia Archives.

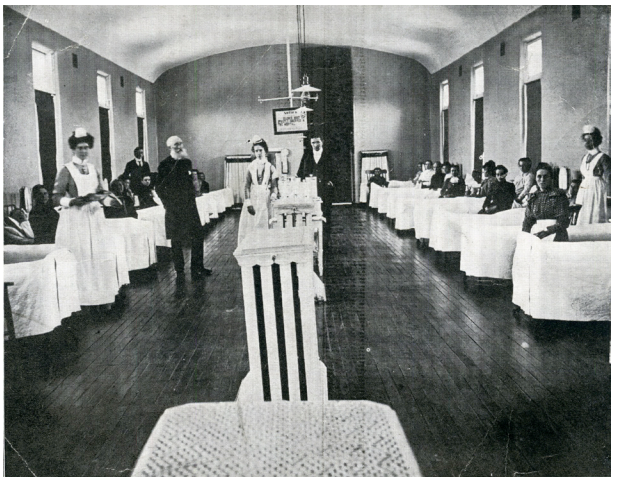

Figure 2: A Victoria General Hospital ward. Photographer unknown. Around 1904. Courtesy of the Dalhousie University Photograph Collection, Dalhousie University Archives, Halifax, Nova Scotia.

who pursued employment in the hospital had actually been discharged by prior employers for drunkenness or other misdeeds. Interestingly, a great deal of "medicine" in the form of wine and spirits were reported to have been consumed by patients, and also conceivably by hospital staff during these early years. Medical care in general remained fairly crude, and common therapies included the liberal use of cathartics and emetics, as well as phlebotomy by venesection or leeching.[5]

In preceding decades, the Poor House offered sufficient clinical volume to support medical education, but its attending surgeon Dr. Bruce Almon jealously guarded his monopoly on these cases, which he tended to reserve for his personal students.[1,3,4] However, with the public hospital now permanently operational, Dalhousie University established a medical faculty in 1868.[5] Financial difficulties forced this program to fold in 1873, but an independent school called the Halifax Medical College then opened in 1875 to take its place.[5,8] That same year, the hospital was scandalized by the "Gleason bodysnatching case" where deceased patients were found to have been used for unauthorized anatomical study.[5] Nonetheless, the legal spectacle and a general public suspicion of the Provincial and City Hospital did not markedly deter sick people from

Figure 3: A Victoria General Hospital ward as seen from Tower Road. The centre Jubilee Building remained in use until its demolition in 1980. Photographer unknown. 1922. Courtesy of the Dalhousie University Photograph Collection, Dalhousie University Archives, Halifax, Nova Scotia.

seeking treatment there. In its first 20 years, it admitted 11 155 patients, largely from poor and working classes.[5] A high proportion of its early admissions were for venereal disease, tuberculosis, rheumatism, and alcohol abuse.

The Victoria General Hospital is Born

The "Great Row of 1885" was a quarrel over political patronage that would lead to major changes at the Provincial and City Hospital. In hiring for the newly-vacant position of house surgeon, the Board of Public Charities selected a politically-favourable candidate over another that the hospital's medical staff rated as superior. The Board of Public Charities obstinately overrode the physicians' protestations, so the entire medical staff resigned in protest.[5,8,9] This action severed the Halifax Medical College's faculty members from their primary source of clinical instruction, and led to a temporary two-year closure of the school.[10]

The controversy dragged on for two years, as several accusations of medical negligence against the new house surgeon and replacement medical staff scandalized the Fielding provincial government.[9] Premier Fielding would eventually abolish the Board of Public Charities and renegotiate ownership of the hospital with Halifax City Council. By an act of the Legislature on May 3, 1887, the province took over complete control of the Provincial and City Hospital, which was then renamed the Victoria General Hospital in commemoration of Queen Victoria's Golden Jubilee.[2,7,9] Hospital management was now the responsibility of the Commissioner of Public Works and Mines, who would oversee the hospital until the creation of the Department of Public Health in 1931.[11]

In the ensuing years, the hospital enjoyed a long period of growth, both in the improvement of its physical infrastructure and the evolution of clinical

medicine as practiced within its walls.[5] In 1888, two long wings were built on the north and south ends of the hospital, boosting capacity from 80 to 140 beds, with some of this construction carried out by Poor House inmates (Figures 2 and 3).[5,8] In 1892, the original building was raised to three levels, in order to expand operating room facilities and add accommodation for privately-paying patients, who were increasingly choosing to receive care there (Figure 4).[6]

Medical education at the Victoria General resumed in 1887, and the Halifax Medical College formalized a relationship with Dalhousie University.[10] 1890 saw the establishment of the Victoria General Hospital School of Nursing, only the third school of its kind in Canada.[5,12] The ongoing professionalization of nursing at the hospital was a tremendous advancement for its patients. The nursing school would operate until 1995, graduating over 3000 nurses during its lifetime.[12,13] While the hospital in 1887 had only two departments, Medicine and Surgery, sophistication of medical care brought further specialization among the medical staff (e.g., organization of the Ophthalmology Department in 1891, Pathology in 1910, Gynecology in 1912). An x-ray machine was installed in 1904,[5] but no organized "X-Ray Department" would emerge until after World War I.[14]

During wartime, the hospital struggled with staffing, as many physicians and nurses served overseas or in military hospitals domestically.[5] On December 6, 1917, the city was rocked by the Halifax Explosion, which shattered many of the hospital's windows.[5,12] Thousands of casualties sought help, either at the established hospitals in the city or at makeshift treatment centres around the community.[15] In total, 575 injured patients were treated at the Victoria General.

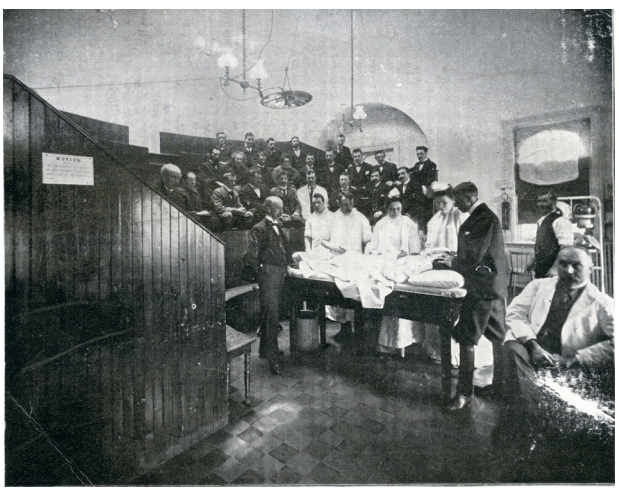

Figure 4: An early operating theatre at the Victoria General Hospital. Sitting in the foreground is pharmacist Charles Puttner, who taught at the Halifax Medical College through its entire life span. Around 1904. Courtesy of the Dalhousie University Photograph Collection, Dalhousie University Archives, Halifax, Nova Scotia.

Far from its beginnings as refuge of last resort for the destitute, by this time the Victoria General regularly received patients from all walks of life. Accordingly, in April 1922, a new 67-bed pavilion was completed, mostly to accommodate privately-paying patients.[16] The distinction between private and public patients would not be eliminated until the advent of state medicine, with introduction of the Hospital Insurance Act (1958) and Medical Services Insurance (MSI; 1966).[5,17] Until then, physicians continued to treat public patients for free, occasionally grumbling about financially-capable patients covertly seeking admission to the gratuitous public wards.[18,19]

In 1931, administrators engaged in preliminary planning for a new hospital but construction of such a facility would prove too expensive during the Depression years.[8] Nonetheless, demand for care continued to rise and the hospital would frequently operate over capacity, a problem that would be exacerbated by another wartime disruption in hospital staffing. In 1935, 6483 patients were admitted.[11] 1943 brought over 7500 admissions, necessitating the construction of a temporary annex to accommodate the overflow.[5] The inadequacy of the original "Jubilee" building for modern medical care became ever more apparent, a factor also thought to be stifling the medical school's growth.[20] Finally, in July 1943, construction commenced on a new hospital building.[5]

The enormous, $2.5 million Victoria Building opened on May 25, 1948.[21,22] Comprising a lofty circular rotunda flanked by three wings, to the north, south, and west, the Victoria Building was the tallest hospital in the British Empire, and the largest building in the Maritimes.[5,23] A new Out-Patients Department was an innovation where patients could pay a small subscription fee to see consultants in clinic for a month without extra charge.[23] This expansion also allowed a previously small, consultative Psychiatry service to start admitting patients for treatment on their own ward.[24]

Further additions to the hospital site would transform the Victoria General into the sprawling complex that it is today. A nurses' residence opened in 1952 (later renamed after long-time administrator Dr. Clarence Bethune).[5,25] The Centennial Building was opened on April 15, 1967, one hundred years to the day of the Provincial and City Hospital's first admission (Figure 5).[26-29] Capacity at the hospital was further increased in 1969 after an extensive renovation of the Victoria Building, to yield a total capacity of 875 beds. The neighbouring Pathology Institute of Nova Scotia and its annex (now the Dr. D.J. Mackenzie Building, and Centre for Clinical Research, respectively) became integrated with the Victoria General in 1974.[30] Finally,

the original Jubilee Building was torn down in 1980 to make way for the six-level Robert Clark Dickson Ambulatory Care Centre, which opened in the summer of 1983.[5,31-33]

In the latter half of the twentieth century, the Victoria General Hospital solidified its status as the major referral hospital in Nova Scotia, and in Atlantic Canada. It became home to a new array of specialist services, such as: Cardiovascular Surgery, Thoracic Surgery, Plastic and Reconstructive Surgery, Orthopedic Surgery, Neurosurgery, Oral and Maxillofacial Surgery, Otorhinolaryngology, Urology, Gynecological Oncology, Cardiology, Gastroenterology, Neurology, Respirology, Psychiatry, Diagnostic Radiology, Nuclear Medicine, Toxicology, Emergency Medicine, and Preventative Medicine.[5,12,26,30,34,35] In 1958, television audiences marvelled at the live broadcast of a patent ductus arteriosus surgical repair in an 8-year old patient, a high-visibility demonstration of the life-changing work carried out in the hospital.[36] The 1960s saw the introduction of a Burn Unit and a Hemodialysis Unit, as well as the inauguration of a kidney transplant program in 1969.[5] The transplant program later expanded in 1985 with its first liver transplant, then its first heart transplant in 1988.[12] Bone marrow transplantation was subsequently started in 1993.[37]

In the 1970s, a series of labour disputes troubled the institution. A mass resignation of over 700 nurses in September 1973 brought the hospital to a standstill for five days, until a settlement with the provincial government resulted in steps to improve working conditions and benefits.[5,38,39] In January 1975, the hospital's medical technicians also resigned in protest, but they were markedly less successful in forcing a quick settlement from the province.[5,30,40,41] The hospital still functioned at over 80% capacity during the technician dispute, though its radiologists were sufficiently incensed by the disruption to their department that they in turn filed a civil suit against the Victoria General. A final strike in 1979, by non-medical staff (e.g., laundry, dietary, and housekeeping), resolved with even fewer concessions from the province.[42]

Figure 5: Aerial photograph of the Victoria General Hospital, with new Centennial wing. The Grace Maternity Hospital can be seen Summer Street, adjacent to the Sir Charles Tupper Building. The roof of the Jubilee Building is visible directly west of the Victoria Building. The Halifax School for the Blind is noted on the opposite side of Tower Road; this is now a parking lot. Photographer Halifax Fire Department. ca. 1970. Courtesy of Halifax Municipal Archives (Accession #102-111-4-6.21) and copyright holder Communications Nova Scotia.

By the 1980s, government management of the hospital was increasingly perceived as ineffective and bureaucratic.[43] A 12-member, province-appointed Board of Commissioners oversaw the institution. Aspects of its daily operations were directly administered by at least five separate government departments. Employing over a quarter of the Nova Scotian civil service, the Victoria General was described at times as the only tertiary care hospital in the country with such an intimate and awkward relationship with its provincial government.[35,43,44] This "maze of government control" was criticized by the 1988 Royal Commission on Health Care, with one member stating "Christ himself couldn't run that organization the way it's set up."[45]

Through the 1980s, the provincial Auditor General repeatedly faulted the hospital's financial management.[46] Although direct government administration of the Victoria General may have sufficed in its earliest years, when the hospital was small and the practice of medicine still nascent, the institution was now far too large to manage in this fashion. The dramatic increase in hospital staffing and services is reflected in its $130-million operating budget in 1985, orders of magnitude greater than that required a century ago (e.g., $38 000 in 1892).[5]

1989 ushered in the beginning of an ambitious, multi-year transition plan toward self-governance of the Victoria General; the hospital would completely sever ties with the provincial government, except for the Department of Health and Fitness.[13,47,48] This plan was not without controversy, as provincial opposition critics conflated hospital self-governance with "privatization," and stoked fears of further diminished accountability.[47,49] Having long been civil servants, Victoria General Hospital workers also feared decreased wages and loss of benefits once they ceased to be directly employed by the government.[47]

The new, streamlined Victoria General administration tackled the hospital's longstanding budgetary deficits, which had previously been absorbed into the provincial debt without much notice.[43] Efforts were made to reduce unnecessary duplication of services, for example by integrating laboratory services

with Camp Hill Medical Centre (or, new Halifax Infirmary).[50] Worries of layoffs and bed closures did materialize in the early 1990s as the provincial government further imposed reductions in the hospital budget.[51-56] The new management also worked to usher in a new institutional culture, that supported further physician involvement in hospital administration, while promoting a model of Continuous Quality Improvement driven by front-line workers.[57,58]

After Amalgamation

In the mid-1990s, the Victoria General Hospital would be pulled into the amalgamation of Halifax hospitals to form the Queen Elizabeth II Health Sciences Centre.[59] The long-awaited new Halifax Infirmary had been envisioned as a full-service community hospital, with the assumption that the Victoria General would continue as the province's major referral centre. Instead, the Victoria General, Halifax Infirmary, Nova Scotia Rehabilitation Centre, and the Nova Scotia Cancer and Research Centre became subsumed into a massive organization that some suspected would be "too unwieldy to manage."[60] The amalgamation generated new anxieties of job losses among Victoria General workers,[61] while pay disparities between the different hospitals[62] and concerns about fairness in hiring for leadership positions also contributed to a sense of discontent that would simmer for years.[63] A previously-proposed $60 million critical care and emergency medicine expansion at the Victoria General site would also be scrapped in favour of consolidating emergency care at the new Halifax Infirmary.[64]

In its final year as an independent hospital, the Victoria General employed 3 000 people, took in 21 838 admissions, and performed 23 201 surgeries.[12] Up to this time, the hospital had transplanted 136 kidneys, 62 livers, and 54 hearts. Though highly-specialized care continued at the Victoria General as it had before, the ensuing decades would see the hospital's profile slowly diminish, while aging and failing infrastructure more frequently captured the public imagination. A medical waste incinerator upgrade in 1992 was subject to criticism for failing emissions standards, and remained the subject of complaints across South End Halifax for years after.[65-69] The Victoria General water supply, contaminated with Legionella since the 1980s, proved resistant to decontamination efforts; at least one patient death, in 2005, was directly attributed to this, and today patients still rely on a bottled water supply.[70] In September 2015, a flood affecting the Intensive Care Unit and other areas led to an emergent relocation of 50 patients, as well as postponement of over 100 surgeries.[71-73] As recently as February 2019, surgeries were again cancelled, and critically ill patients transferred, on account of issues with the hospital power supply.[74] The increasingly decrepit nature of the Victoria General is now a common grievance.[75-77]

Figure 6: The Centennial and Victoria Buildings as they appear now. The differently-coloured brick on the Victoria Building reflect later additions from the original 1948 structure. Photographer Mike Wong. 2019.

In 2011, the provincial government under Premier Dexter announced its intention to demolish the Centennial and Victoria buildings over five years, with specialized services likely consolidating at the Halifax Infirmary site.[78,79] Yet today, the Victoria and Centennial Buildings are still heavily in use, as plans for reorganizing and redeveloping the QEII Health Sciences Centre remain in flux.[80-83] The reorganization of services currently offered at the Victoria General is an immensely complex and expensive task, even in early planning stages,[84] with the final execution currently estimated to cost $2 billion.[85,86]

From its humble beginnings aiding Halifax's most downtrodden and undesirable, the Victoria General Hospital weathered political machinations beyond its control, to birth a well-regarded medical school and itself become the region's towering giant of medical progress. Surely, the city's early physicians who lobbied for a public hospital would never have dreamed of the wonders that now take place there every day. Though recent history has seen the Victoria General's standing diminish, this under-appreciated and unfortunately maligned institution has elevated the health of Nova Scotians for well over a century, and that is a legacy to be proud of.

Acknowledgements

Many thanks to Dr. Bernard Badley, Dr. Jock Murray, and Dr. Allan Marble, for providing editorial feedback and invaluable sources for this piece. All Nova Scotians are indebted to the long history of charitable works by the physicians, nurses, allied health professionals, and non-medical staff at the Victoria General Hospital.

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Case report

Severe thrombocytopenia in an adolescent caused by Epstein Barr Virus

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Introduction

Infectious mononucleosis is an acute disease caused by the Epstein-Barr virus (EBV) and characterized by sore throat, fever, lymphadenopathy, splenomegaly and atypical lymphocytosis. It typically has a benign course and lasts approximately 3 weeks, but fatigue can persist for months. Serious complications, including death, have been reported but are rare.[1,2] Accounts of a bleeding diathesis associated with this disease have long been observed.[3] Hematologic complications of EBV include neutropenia in 50-80% of cases and hemolytic anemia in approximately 3% of cases.[1] Mild thrombocytopenia occurs in 25-50% of cases, but severe thrombocytopenia with platelet counts less than 20 x 10^9/L is rare.[1] An earlier publication that reviewed cases between 1965 and 1997 identified 37 patients with this complication.[2] Our own MEDLINE search of "acute Epstein-Barr infection and severe thrombocytopenia" from 1998 until 2018 identified an additional seven cases.[4-8] We herein report a case of an adolescent who presented with platelet levels of 3 x 10^9/L in the setting of an acute EBV infection. Given that there are few reports of this rare complication in the literature, and the vast majority of reports were published over a decade ago, it would be prudent to educate current physicians on the possibility of an exceedingly low platelet count with this common viral illness and furthermore highlight the need to assess for an EBV syndrome in patients presenting with severe thrombocytopenia.

History

A 19-year-old Caucasian male student presented to the Halifax Infirmary Emergency Department with an approximate one-week history of fever, chills, sweats, nausea, abdominal pain, headache and nasal congestion. He had also lost about 10 lbs in the preceding 2-3 weeks when his appetite began to decline. His past medical history was significant for gastroesophageal reflux disease and for this he took pantoprazole 40mg orally once daily. His only other medication was ibuprofen as needed prior to playing hockey.

Examination

On presentation, his vital signs were within normal limits with a temperature of 37.6°C. He had wet purpura in his mouth and petechiae present on the thorax and dorsal aspects of his feet and arms. He had tender head and neck adenopathy and inflamed tonsils. His abdominal exam revealed splenomegaly. Cardiac and respiratory examinations were unremarkable.

His initial complete blood cell count showed a haemoglobin of 141g/L, WBC 15.85 x 10^9/L and platelets of 3 x 10^9/L. Platelet levels from previous bloodwork were within normal limits. Blood smear revealed severe thrombocytopenia with >70% atypical lymphocytes. Peripheral blood flow cytometry later showed reactive lymphocytes without a clonal population. INR was 1.1 and PTT 33 seconds. Liver testing showed a hepatitis with ALT 439 U/L, AST 267 U/L, ALP 299 U/L, GGT 181 U/L, with normal total bilirubin at 5.2 U/L. Hepatitis B surface antigen was negative and surface antibody was positive. Hepatitis C antibody, hepatitis A IgM, and HIV were negative. CMV IgG was positive. Blood cultures were negative. Anti-EBV nuclear antigen (EBNA) antibodies were negative and viral capsid antigen (VCA) IgM antibody was positive. To illustrate the meaning of these results, note that with the measurement of VCA IgG, VCA IgM, and EBNA IgG, one can distinguish acute from past infection; the presence of VCA IgM and VCA IgG without EBNA IgG indicates acute infection, whereas VCA IgG and EBNA IgG without VCA IgM suggests a past infection. Based on our patient's clinical syndrome and his positive VCA IgM, he was diagnosed with acute EBV and severe EBV-related thrombocytopenia.

Treatment/Course in Hospital

The patient was admitted to the Medical Teaching Unit and was cared for by the General Internal Medicine team with Hematology in consultation. He experienced one episode of epistaxis (relieved with pressure), as well as one episode of minimal hematochezia and hematemesis. His hemoglobin dropped from 141 to 126g/L, thus never necessitating a blood transfusion. His symptoms improved overall during his five-day admission. With regards to treatment, please see Figure 1 for a timeline and corresponding platelet levels. He was transfused with platelets to a threshold of 10 x 10^9/L. On days 2 and 3 of his admission, he was treated with intravenous immunoglobulin (IVIG, Figure 1). On day 4, he was started on a 5 day course of prednisone at 50mg/day and was discharged home on day 5 with platelets at 32 x 10^9/L. Approximately one week after

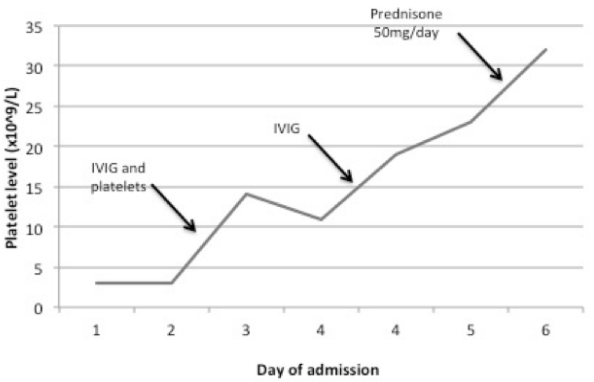

Figure 1: Timeline of treatment and platelet response in the in-patient setting for our case of severe thrombocytopenia in the setting of acute EBV infection.

completing his prednisone course, he presented to the Emergency Department a second time with ongoing thrombocytopenia (platelets 32 x 10^9/L) and persistent symptoms of mononucleosis (fatigue, malaise and dyspnea). He was given a longer course of prednisone, starting at 1mg/kg and tapered over a period of approximately 2 months, and his platelets recovered to normal values by the end of his prednisone course.

Discussion

Mild thrombocytopenia from acute EBV infection can occur in up to 50% of adult patients. From the literature, it would appear that individuals who develop severe thrombocytopenia secondary to acute EBV infection tend to be less than 21 years of age, and in such individuals platelet count nadirs below 10 x 10^{10}/L can occur more frequently than one might expect.[2] Of the 37 cases identified by Pipp et al with platelet counts below 20 x 10^{10}/L, 75.7% were 21 years of age or younger and 78.4% of the 37 cases developed platelet counts below 10 x 10^{10}/L.[2] Of the patients that developed serious complications, 80% had counts below 10 x 10^{10}/L. Our patient was 19 and had severely low platelets but did not suffer any serious sequelae.

While severe thrombocytopenia complicating infectious mononucleosis may resolve spontaneously within days to weeks, treatment may be required.[9] The mainstay of treatment, which is corticosteroids, often follows the guidelines for managing primary immune thrombocytopenia purpura as specific guidelines for viral induced thrombocytopenia are poorly defined.[10] However, response to corticosteroids may take weeks.[2] Platelet transfusions can be used supportively but the effect is only temporary. IVIG should be used in the case of presence of extensive purpura or internal bleeding.[10,11] IVIG can also be considered without extensive purpura or bleeding in the context of a platelet response below 5 x 10^{10}/L that has not responded to corticosteroid therapy.[10,11] The presence of extensive purpura in our patient justified the use of IVIG as a first line therapy. The two doses of IVIG helped his platelets recover to near 20 x 10^{10}/L. Methylprednisone pulse therapy and high dose dexamethasone have also been used in cases where an urgent increase in platelets was necessary or platelet levels were refractory to corticosteroids.[12,13] Refractory cases despite glucocorticoid/IVIG therapy with ongoing bleeding complications are considered for splenectomy, rituximab or thrombopoietin receptor antagonism. Importantly, it is necessary to avoid any drug that interferes with platelet function, such as aspirin and nonsteroidal anti-inflammatory agents. The majority of cases with thrombocytopenia recover from this acute complication. The development of chronic thrombocytopenia is possible but rare.

Various mechanisms have been proposed to explain thrombocytopenia with acute EBV infection. Autoimmune responses to the virus can generate antibodies against platelet membrane glycoproteins in about 40% of patients.[2] Splenic sequestration secondary to hypersplenism has also been proposed as an additional mechanism, however patients with severe thrombocytopenia may have normal spleen sizes, and those with splenomegaly may have normal platelet counts.[5] Lastly, it has been proposed that in cases of thrombocytopenia purpura secondary to EBV, antiplatelet factors may be contributing to very short isologous platelet survival.[14]

In conclusion, severe thrombocytopenia secondary to acute EBV infection occurs rarely, but can lead to serious complications, typically in young adults and children. Acute EBV infection should be considered as a potential cause in patients with undifferentiated thrombocytopenia and a compatible clinical syndrome, while ruling out lymphoproliferative disease. If severe thrombocytopenia is confirmed to be secondary to EBV, corticosteroids are the mainstay of treatment. In cases where immediate platelet recovery is necessary, IVIG, pulse steroid therapy and supportive platelet transfusions can be used.

Consent

Written consent to publish this case report was obtained from the patient. The consent was fully informed, voluntary, written, and is within the possession of Dr. D. Haase.

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