We would like to give our sincerest thank you to the Keenan family for your continuous support to our research students and the Keenan Research Summer Student Program. Furthermore, thank you to the Principal Investigators and research staff for your interest in the KRSS program and for mentoring and supporting these students. As a result of your guidance, students have gained a much deeper understanding of research and its impact.
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## Basic Science

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Role of miRNA-26a as a Potential Therapy for Abdominal Aortic Aneurysms

Tsilker, Tiffany; Czerwoniak, Maya; Elfaki, Lina; Kuliszewski, Michael and Leong-Poi, Howard
Department of Cardiology, St. Michael’s Hospital, Toronto, Ontario

Background: Abdominal Aortic Aneurysms (AAA) are characterized by a marked dilation and weakening of the abdominal aortic walls. Destruction of the extracellular matrix (ECM) in the aortic wall and increased apoptosis of vascular smooth muscle cells (VSMCs) contribute to the compromised wall integrity observed in AAA patients. Additionally, abnormal neovascularization and angiogenesis of endothelial cells (ECs) due to an increased inflammatory state contribute to the expansion of the aortic wall. MicroRNA-26a (miR26-a) is an anti-angiogenic, known regulator of VSMC function and is downregulated in AAA.

Hypothesis: In our in-vitro AAA model, VSMCs transfected with miR-26a will undergo increased proliferation and transfected ECs will exhibit an anti-angiogenic effect.

Methods: In-vitro, haSMCs were stimulated with IL-1β (20ng/ml) in order to mimic the pro-inflammatory state associated with AAA. Then, haSMCs were transfected with miR-26a, antimir-26a or scrambled-control mir to demonstrate the molecular effects of miR-26a. Similarly, ECs will be stimulated with IL-1β and then transfected. Transfected ECs will be utilized in a Matrigel assay to quantify their angiogenesis. p<0.05 was considered significant.

Results: In-vitro, previous work showed that IL-1β downregulated miR-26a (0.30±0.05) in haSMCs and transfection was confirmed using qRT-PCR (71.5±9.5) and FACS assay (75.3±1.7%). In our experiments, we observed decreased levels of differentiation markers, α-smooth muscle actin (ACTA2; 0.56±0.06) and Transgelin (TAGLN; 0.58 ± 0.05) using qRT-PCR. Additionally, there was an observed increase in haSMC proliferation following miR-26a transfection using MTS assay.

Conclusion: The in-vitro model showed increased proliferation and decreased ACTA2 and TAGLN in haSMCs, suggesting they de-differentiated towards their synthetic proliferative phenotype – which helps restore wall integrity. We are currently investigating the effects of miR-26a on ECs affected by AAA, where we expect to observe an anti-angiogenic effect. In conclusion, these results suggest the potential of a miRNA therapy using miR-26a for AAA patients.
Characterization of the nuclear localization signal of TAZ

Gill, Gary\textsuperscript{1,2}; Kofler, Michael\textsuperscript{2}; and Kapus, Andras\textsuperscript{1,2,3,4}

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Forty-five \% of deaths in the western world are associated with tissue/organ fibrosis, while 30\% of Canadians die from cancer. Yap and TAZ are transcriptional co-regulators involved in cell proliferation, development and regeneration, and their dysregulation is implicated in fibrosis and cancer. The nucleocytoplasmic shuttling of Yap/TAZ is regulated by the hippo pathway and mechanotransduction via the actin cytoskeleton. Previous studies have defined TAZ’s nuclear and cytoplasmic retention factors, TEAD and 14-3-3, respectively, but the nuclear localization signal (NLS) of TAZ and the mechanism underlying its nuclear transport remained unknown. Our lab has recently defined the TAZ NLS as a non-classical, negatively-charged 15-mer sequence that is sufficient to mediate Ran GTPase-independent nuclear accumulation of artificial cargoes. Here we aimed to define the specific amino acids critical for TAZ nuclear accumulation and to obtain kinetic evidence that this 15-mer NLS indeed mediates nuclear import. To achieve this goal, three mCitrine (3C) molecules were fused to the TAZ NLS to eliminate nuclear entry via passive diffusion. Nuclear import was studied using fluorescence recovery after photobleaching (FRAP). Nuclear fluorescence recovery was significantly slower for the 3C tag alone (control) compared to the 3C-TAZ NLS, which could be fitted with a monoeponential curve. Mutational analysis of the NLS revealed that, in addition to the key role of negative residues, a particular methionine is also indispensable, as a single methionine-to-valine (M337V) mutation nearly abolished nuclear import. Moreover, the TAZ NLS potently inhibited the nuclear import of cargoes mediated by classic, positively charged NLS, such as the prototypical example in simian virus 40. Identification, kinetic and mutational characterization of this new NLS class paves the road not only for unraveling the underlying transport mechanism, but also for discovery of new drugs that inhibit TAZ import and thereby exert therapeutic potential to lessen fibrosis and cancer.
A Novel Hybrid Tracer for In Vivo Photoacoustic Imaging and Ex Vivo Fluorescence Imaging

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INTRODUCTION: QC-1, a near infrared (NIR) dark quencher dye, conjugated to bovine serum albumin (BSA) has been used to study lymphatic drainage of aqueous humour from the eye to the cervical lymph nodes (CLNs) through in vivo photoacoustic imaging (PAI) in mice.¹ Ex vivo validation of tracer in the eyes and CLNs was conducted on separate mice using CF770, a NIR fluorescent dye.¹ Purpose: To design a tracer that allows in vivo photoacoustic imaging and ex vivo fluorescence imaging validation to be conducted in the same mouse.

METHODS: BSA was labelled with QC-1 and a fluorescent dye (pentamethyl BODIPY). 2 μL of tracer (500 μM QC-1) was injected into the right anterior chamber of each CD-1 albino mouse (n=3). Lymphatic drainage of the tracer to the CLNs was visualized using in vivo PAI. Following sacrifice, a confocal scanning laser ophthalmoscope (cSLO) was used to image the heads to detect BODIPY fluorescence signal. Selected cryosections of the eyes and CLNs were counterstained with DAPI and examined for the distribution of BODIPY using confocal microscopy.

RESULTS: The absorption spectrum of the hybrid tracer was comparable to that of QC-1/BSA used in previous studies for PAI and has an additional absorption peak at 503 nm corresponding to the BODIPY dye. Strong tracer signal was observed in the right eyes and CLNs of all mice in in vivo PAI. cSLO and confocal microscopy detected fluorescence signal in the right eyes but not in the CLNs for all mice.

CONCLUSION: Tracer drainage from the eyes to the CLNs was evident in in vivo photoacoustic images. Lack of ex vivo fluorescence signal in the CLNs suggests that the BODIPY dye may have detached from the BSA and remained in the ocular tissues. Other fluorescent dyes with greater affinity to BSA should be used to improve the hybrid tracer for ex vivo fluorescence imaging.
Industry Funding and Editorial Financial Conflicts of Interest in Randomized Controlled Trials

Nath, Nikhil; Montagnese, Basile; Elsolh, Karam; Khan, Rishad; Scaffidi, Michael; Gimpaya, Nikko; Grover, Samir C.

Division of Gastroenterology, St. Michael’s Hospital

INTRODUCTION: There is a high prevalence of journal editors who have financial relationships with industry sponsors. Prior studies have not been conducted on the association between editorial financial conflict of interest (FCOI) and the publication of industry sponsored randomized controlled trials (RCTs). We examined payments made to editors of journals by industry sponsors of RCTs published in the corresponding journals.

METHODS: We identified all phase III RCTs (N=757) evaluating a medication or device published from January 1 2014 to December 31 2017 using a modified version of the Cochrane highly sensitive search strategy in MEDLINE. The journal and issue of each RCT was identified. From the issues, we extracted a list of editors from the journal mastheads. Industry payments made to journal editors were identified using the Centre for Medicare and Medicaid Services (CMS) Open Payments Database, which collects data on payments provided by commercial entities to physicians. All data were presented descriptively as median and interquartile range (IQR).

RESULTS: Based on a preliminary analysis of 458 trials, we found that the total dollar value of the COIs was $10,702,874.19. The median conflict dollar value was $4,959.92 (IQR: $110.69 to $19,524.93).

CONCLUSION: We found a high burden of FCOI among journal editors that have published phase III RCTs. This finding is concerning as FCOI have been associated with publication bias. Given their responsibility to impartially publish RCTs, editors should ensure greater transparency with industry relationships.
Identifying Fibro Adipogenic Progenitors (FAPs) in long-term denervated Muscle

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Purpose and Significance: A key feature of long-term denervation-induced muscle injury is the progression of fibrosis. In injury models such as acute direct injury (toxins), as well as dystrophy, fibrosis has been attributed to an up regulation of Fibro-Adipogenic Progenitor (FAP) cells. In long-term denervated muscle, the cellular mediators of fibrosis are currently unclear. The purpose of this project is to identify whether or not FAP cells are responsible for the fibrosis observed in long-term denervation injury. Specifically, we expect to see a sustained up regulation of FAP cells post-denervation compared to healthy controls.

Summary of Results: We have developed and optimized a method for identifying FAP cells from rat skeletal muscle via flow cytometry. Through this method we have identified an up regulation of FAPs following denervation up until 5 weeks post injury. To confirm these results, we aim to identify FAP cells in an acute injury model and compare their dynamics to our long-term denervation model. We anticipate seeing a transient increase in FAPs in the acute model before returning to baseline levels.
Role of Dapagliflozin in Attenuating Right Heart Failure: Chronic Overload Model Mechanistic and Translational Studies

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This project is supported by The Keenan Research Summer Student Program

BACKGROUND: Chronic heart failure is a massive problem in industrialized nations and is projected to increase by 46% over the next 20 years. Many patients undergoing primary right ventricle (RV) failure have secondary left ventricle (LV) failure due to geometric changes in the RV. Therefore, heart failure (HF) might be better considered as a biventricular disease. Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor that has recently been shown to improve heart function in the setting of diabetes. We hypothesize that by inducing chronic volume overload, by the administration of deoxycorticosterone acetate (DOCA), dapagliflozin will attenuate cardiac remodelling, by reducing excess fluid volume, right ventricular chamber dilatation, and wall tension.

METHODS: 7 week old Male Sprague-Dawley rats weighing 180-200g underwent unilateral nephrectomy (UNX) surgery. After one week, rats were randomly selected to either serve as controls, or receive DOCA salt implant. DOCA rats received 1% saline as drinking water. Subsequently, rats were further randomized to receive treatment with dapagliflozin, vehicle, or spironolactone, which served as a positive control. This created six experimental groups.

EXPECTED RESULTS: We expect that dapagliflozin treated rats will have improved RV chamber function due to a reduction in fluid volume and a decrease in hypertrophy. Through the use of bioimpedance spectroscopy (BIS), we predict that vehicle treated rats have an increase in total body water when compared to the dapagliflozin rats. After animals are sacrificed, and tissue collection is complete, morphologically, DOCA-salt treated animals should display an increase in LV and RV weight, as well as an increase in lung weight when compared to control animals.
Title: Targeting N-type calcium channels to prevent opioid-induced respiratory depression and find safe opioid pain therapies

Authors: Lauren Levy¹, Shenhab Zaig¹, Samantha Mahabir¹, Carolina Scarpellini¹, Gaspard Montandon¹,²

Affiliations: ¹Keenan Research Centre for Biomedical Science, St. Michael’s Hospital ²Division of Respirology, Department of Medicine, University of Toronto

Background & Rationale: In 2018, Canada experienced 4,460 opioid-related deaths. While opioid drugs are potent analgesics, they can induce respiratory depression and can be lethal with overdose. Opioid drugs inhibit neural circuits by activating the G-protein coupled µ-opioid receptors (MORs). One of the key-channels mediating MOR-related inhibition is N-type voltage-gated calcium channels, which are inhibited by MORs. The roles of these N-type calcium channels in opioid-induced respiratory depression and opioid analgesia are unclear. Larval zebrafish have neural respiratory circuits similar to mammals and their MORs share 74% homology. Having previously established a model for opioid-induced respiratory depression and analgesia in larval zebrafish in our group, we aim to determine the role of N-type calcium channels in mediating opioid-induced respiratory depression and analgesia. Here, we propose that the opening of N-type calcium channels by the calcium channel opener nefiracetam will reduce the effects of opioids on breathing and pain. Methods: Respiratory depression was assessed by measuring buccal movements, as an index of respiratory activity, in response to the opioid analgesic fentanyl in zebrafish larvae 12-14 days post-fertilization. Zebrafish were randomized into treatment groups: control, fentanyl (1μM) or fentanyl (1μM) + nefiracetam (1μM). To determine whether nefiracetam can block the analgesic effects of fentanyl, we will assess the impact of fentanyl on the nociceptive swimming response to the pain stimulus formalin (0.05%) with and without the application of nefiracetam. Future Directions: Opioid drugs are widely used for pain management, but their use is limited by the risks of respiratory depression and fatal overdose. Here, we aim to determine whether targeting N-type calcium channels may provide potential targets to alleviate respiratory depression while preserving opioid analgesia. If nefiracetam can block respiratory depression without altering analgesia, it may constitute an adjunct treatment to opioid analgesics to prevent respiratory depression. Other doses and N-type calcium channel agonists will better elucidate the role of this channel.

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The Keenan Research Summer Student Program - Neurovascular Database Project

Uddin, Mohammad Aziz \(^1\); Dayyani, Faranak \(^2\); and Bharatha, Aditya \(^1\)

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St. Michael’s Hospital uses an outdated and primitive booking software known as Soarian Scheduling. In its current state, Soarian is unable to adequately resolve clerical issues that the Neurovascular clinic (NV) faces on a daily basis. In order to resolve the issues that Soarian is unable to fix, the NV clinic has resorted to using a paper based method in order to adequately book patients and store information about them. This paper based method has proven to be highly inefficient and ineffective as it is very time-consuming and disorganized. Using the diverse functionalities of Microsoft Access, a database management system, Dr. Aditya Bharatha’s team and I have created a versatile and robust software system that is able to successfully track patient appointments and information. In using this software system, we aim to reduce the time to book patient appointments, increase the organization of patient information and increase efficiency in the NV clinic. We are currently in our beta testing phase where we have given a software prototype to the Neurovascular clinic to test and their feedback will allow us to continue to improve our system.
Perception of Non-Technical Skills in Gastrointestinal Endoscopy: A Thematic Network Analysis of Four Focus Groups

Abiramy Thayanantha, Jeevanjot Dhillon, Michael A. Scaffidi; Rishad Khan; Catharine M. Walsh; Eric Lui; Nikko Gimpaya; Shai Genis; Samir C. Grover

INTRODUCTION: Non-technical skills (NTS), which are skills that involve an individual’s cognitive, attitudinal and social skills, have an impact on the quality of gastrointestinal (GI) endoscopic procedures. We aim to explore the NTS relevant to GI endoscopy using a series of focus groups conducted at tertiary care.

METHODS: We conducted four focus groups to determine relevant NTS to GI endoscopy among three groups of pertinent stakeholders: physicians who perform endoscopy; endoscopy nurses; and patients who received a recent endoscopy. A fourth focus group was conducted with both physicians and nurses to ensure agreement between themes generated by each separate group. The findings were analyzed using thematic network analysis to determine the salient NTS relevant to GI endoscopy.

RESULTS: A preliminary analysis found that there were six NTS relevant to GI endoscopy: teamwork; communication; decision making; situational awareness; leadership; and professionalism.

CONCLUSION: Our findings that identify important NTS in GI endoscopy provide a framework for future education interventions and assessment of competency.
Salvia miltiorrhiza root (Danshen) extracts have been widely used in China for the treatment of cardiovascular diseases. Danshen depside salts have been approved for treatment of coronary heart disease and chronic angina in China in 2005. Salvianolic acid B (SAB) is the most abundant bioactive compound in Danshen, however, its mechanism of action is not yet adequately understood. A better understanding of SAB will improve its use and prevent adverse drug interactions. Previously, our lab has shown through structural analysis that SAB bears similarities to trisubstituted benzimidazole class of thrombin inhibitors, including dabigatran. In silico molecular modeling predicted that SAB binds to similar residues as dabigatran within the thrombin active site and acted as a competitive thrombin inhibitor. We have also shown that SAB can inhibit blood coagulation using a series of in vitro coagulation assays. SAB delayed the initiation of coagulation in human cell-free plasma using thromboelastography, significantly reduced clot weight in human whole blood, and reduced fibrin network density in cell-free murine plasma using scanning electron microscopy. Currently, we have demonstrated that SAB can decrease ADP-, collagen-, and thrombin receptor activating peptide-induced human and murine platelet aggregation. Interestingly, SAB is a potent inhibitor of thrombin-induced platelet aggregation, in comparison to other agonists. Using human whole blood, SAB can decrease platelet adhesion on collagen in ex vivo perfusion chambers at high shear rates (1,800s⁻¹). Furthermore, using our intravital microscopy laser injury thrombosis model, we have demonstrated that SAB significantly decreases murine thrombus growth in vivo. Collectively, these data establish a novel mechanism of action for SAB in the inhibition of both platelet aggregation and blood coagulation, likely through direct thrombin inhibition. These unique characteristics position SAB as safe and potent herb-derived anti-thrombotic agent. Funding Agencies: Heart and Stroke Foundation, Canadian Blood Services, Canadian Institutes on Health Research
Characterization of Endothelial Progenitor Cells and Their Role in Treatment of Fracture Non-Unions

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Sponsors: Keenan Research Summer Student Program, Orthopaedic Trauma Association

Fracture non-union, the failure of bone healing within an expected time period, poses a significant challenge in orthopedic surgery and is a substantial burden to patients. Infection and poor vascularization often play a large role in fracture non-union, and novel therapeutic approaches aim to address these issues. Endothelial Progenitor Cells (EPCs) are stem/progenitor cells, isolated from circulating blood, bone marrow, or umbilical cord blood,1 that have vasculogenic and angiogenic properties.2 Clinical trials indicate that EPCs may be promising candidates for the treatment of many diseases in the fields of ischemic vascular disease and vascular regenerative medicine, like coronary artery disease and myocardial infarct, peripheral occlusive vascular disease, diabetic microvasculopathy, and critical limb ischemia.2 Recent research has shown that EPCs isolated from bone marrow are a potential treatment of fracture non-union in animal models.3 Despite their therapeutic promise, EPCs are poorly defined and characterized, and their use in fracture non-union in infected hosts is still under investigation. This study aims to characterize surface markers and to investigate vasculogenic and osteogenic properties of EPCs derived from rat bone marrow. Investigative methods include flow cytometry, Matrigel-based tube formation and antibiotic-response assays, and serial radiographs following surgery to create femoral defects and insert EPC-loaded scaffolds into the defect of infected rats treated with local antibiotics. The findings of this study could serve to facilitate the translation of basic science into clinical practice and, eventually, may lead to improved patient care.
Investigating the mechanisms of cardio-protection exhibited by Empagliflozin and liraglutide using the Goto kakizaki rat a non-obese model of T2D.

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Diabetes, while a devastating disease on its own, has many equally devastating complications. Cardiovascular complications are responsible for three quarters of diabetic patient deaths. Thus, it is important to investigate the cardiovascular effects of novel and current therapeutic diabetes interventions. In the present study, we investigate two type 2 diabetes (T2D) drugs, Empagliflozin and Liraglutide. Empagliflozin is a selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor that lowers rates of hyperglycemia in patients with T2D by decreasing renal glucose reabsorption and increasing urinary glucose excretion. Liraglutide is a Glucagon-like peptide-1 (GLP-1) receptor agonist that lowers postprandial hyperglycemia by increasing insulin release from the pancreas and decreasing excessive glucagon release. The drugs differ in their mechanisms of action, Liraglutide is insulin dependent, whereas Empagliflozin is not. However, both have demonstrated cardioprotective properties. Here we investigate the potential causes of the observed cardiovascular effects of the two drugs using a clinically relevant model of T2D—the non-obese, non-hypertensive Goto Kakizaki (GK) rat. Male GK rats were aged to 40 weeks and were treated with Empagliflozin, liraglutide or control (Saline) for 8 consecutive weeks (32-40wks). Cardiac structure and function were assessed by echocardiography and pressure-volume loops at baseline and end study. Left-ventricular tissue samples were also collected for histological and molecular analysis. Our data has demonstrated that the cardiac protection offered by these drugs does not involve Il-1beta and the NLRP3 inflammasome. Additionally the use of Il-1 beta inhibition may be beneficial to reduce residual cardiovascular risk in diabetic patients using these therapies.
Transplantation of type II alveolar epithelial cells generated from induced pluripotent stem cells as treatment in a rat model of lung injury

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The alveolar epithelium is comprised of two cell types: type I alveolar epithelial cells (AECI), which participate in gas exchange, and type II alveolar epithelial cells (AECII), which secrete surfactant and are the alveolar stem cells.1 Acute respiratory distress syndrome (ARDS), characterized by damage to this alveolar epithelium, results in pulmonary edema and shortness of breath. ARDS is treated through oxygen therapy and supportive care. ARDS patients could also benefit from restoration of their alveolar architecture through tissue engineering efforts. We hypothesize that transplantation of AECII will allow for alveolar regeneration in ARDS-affected rats. AECII, as alveolar stem cells, can proliferate and differentiate to restore the epithelium. To address our hypothesis, ARDS was induced in rats using an acid instillation model, wherein acid causes direct tissue damage, neutrophil activation, and subsequent inflammation. Forty-eight hours after acid instillation, ARDS establishment was assessed by measuring lung elastance and analyzing lung histology. We measured increased elastance and pulmonary inflammation in acid-treated rats, confirming establishment of ARDS. In parallel, AECII for treatment were generated from induced pluripotent stem cells (iPSCs) using a forty-five-day differentiation protocol, in which select morphogens are supplemented in culture to differentiate the iPSCs into lung progenitor cells and finally AECII. Derived AECII will be surgically implanted into the left lung of ARDS-affected rats. Following surgery, the rats will be monitored for improvement of symptoms for up to six months post-operation. Lung function and histology will be compared between ARDS-affected rats that underwent AECII implantation to those that did not. This study hopes to provide evidence for the use of tissue engineering in ARDS.


Funded by the CIHR. Submitted to the KRSS Program.
Immune thrombocytopenia (ITP) is an autoimmune disorder commonly caused by autoantibodies against platelet surface proteins GPIIbIIIa and/or GP1bα, leading to severe thrombocytopenia and potentially fatal bleeding. 70-80% of ITP patients have autoantibodies against GPIIbIIIa, leading to Fc-dependent platelet clearance by splenic macrophages. Anti-GPIIbIIIa thrombocytopenia responds well to steroids, IVIG, anti-RhD, or splenectomy. Most patients with anti-GP1bα autoantibodies, however, are resistant to these therapies. Our lab has discovered that anti-GP1bα instead induces an Fc-independent platelet activation, surface expression of neuraminidase-1, and subsequent desialylation of GP1bα in a positive feedback manner. These desialylated platelets are cleared via Ashwell-Morell receptors on hepatocytes leading to thrombocytopenia. This distinct pathway of platelet clearance is amendable to sialidase inhibition in mice, offering a potential therapeutic target for refractory ITP patients.

Conversely, some patients have an antibody-independent ITP marked by decreased immunosuppressive CD8+ Tregs and increased CD8+ cytotoxic T lymphocytes (CTLs). These CTLs release proinflammatory cytokines and cytolytic granules into the circulation and bone marrow leading to platelet and megakaryocyte lysis. Clinically, CD8+ T-cell-mediated ITP is often refractory to therapies targeting antibody-mediated pathways, with evidence suggesting CD8+ Tregs transfusion may have therapeutic benefits. Ultimately, deeper investigation into the differential pathogeneses underlying ITP will uncover more specific and focused treatments to ameliorate this life-threatening disease.

Radiogenomic Analysis of Lower Grade Glioma

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The presence of specific genetic markers, namely a codeletion on the chromosomal arms at 1p and 19q, are markers for positive response in lower grade gliomas towards specific types of chemotherapy and radiotherapy\textsuperscript{1}. Identification of these genetic markers allows for design of far more effective treatments plans in patients with lower grade gliomas. In the current status quo, the only method to identify these codeletions is through surgical biopsy and performance of fluorescence in-situ hybridization. Due to the invasive nature of the biopsy procedure, a less invasive method of identification would be extremely beneficial to develop. This project focuses on the construction of a machine learning model using MR imaging in order to identify the presence of this codeletion. Based on a previous Mayo Clinic study\textsuperscript{2}, comparative tests will be run on a variety of different combinations of feature extraction and selection programs, and machine learning models to identify the best such combination for accurate identification of codeletion presence in patient MR images.

References:


Loss of Endothelial Cell-Specific Autophagy-Related Protein 7 Exacerbates Doxorubicin-Induced Cardiotoxicity

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Doxorubicin (DOX) is a broad-spectrum anti-cancer therapeutic that has proven as an effective treatment for many cancers including breast, lung, and thyroid cancers. However, it has been established that the use of DOX may have potent cardiotoxic side effects which may culminate in heart failure. One physiological mechanism for countering such cardiotoxic effects involves endothelial cell-mediated cardioprotection. As such, this study attempts to establish a link between endothelial cell function and the cardiotoxic side effects induced by doxorubicin. Transgenic mice were generated with an endothelial cell specific knockout of Atg7, a protein involved in autophagy – which is a cellular mechanism important to endothelial cell health. Experimental mice, with wild-type or knockout (KO) alleles of endothelial Atg7, were treated with either DOX or a saline solution. It was hypothesized that the Atg7−/− KO mice would develop more severe cardiotoxicity in response to DOX treatment due to reduced endothelial cell-mediated cardioprotection as a result of disrupted autophagy. Experimental results showed that targeted loss of EC-Atg7 expression in mice significantly reduced survivability of DOX-injected mice. This result may be paralleled with the finding that DOX-treated EC-Atg7−/− mice also experienced greater decline in cardiac function as well as greater fibrosis observed in the cardiac ventricles. Studies evaluating the relationship between endothelial cell autophagy and DOX-induced cardiotoxicity are warranted to further establish the supportive role of the endothelium in the prevention of DOX-associated heart failure.

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# Health Science

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Patient and Public Preferences on Being Recontacted with Updated Genomics Results: A Mixed Methods Study.

Sarah Muir1, Christina Di Carlo1, Agnes Sebastian1,2, Chloe Mighton1,2, Marc Clausen1, Salma Shickh1,2, Nancy Baxter1,2, Adena Scheer1,2, Theresa Kim1,3, Dean Regier4, Emily Glogowski5, Kasmintan Schrader6, Raymond H. Kim3,4,5, Jordan Lerner-Ellis2,5, Ahmed Bayoumi1,2, Yvonne Bombard1,2

1St. Michael’s Hospital, Toronto, ON, Canada, 2University of Toronto, Toronto, ON, Canada, 3University Health Network, Toronto, ON, Canada, 4The Hospital for Sick Children, Toronto, ON, Canada, 5Mount Sinai Hospital, Sinai Health System, Toronto, ON, Canada, 6BC Cancer Center, Vancouver, BC, Canada, 7GeneDX, Gaithersburg, MD, USA

Background: A key issue in delivering genomics services is whether patients should be recontacted when new evidence changes their genetic variant’s association with disease. Current guidelines for research recommend participants be recontacted with updates of their genetic testing results. However, individual preferences for recontact, in a clinical or research setting, are not well known. Aim: Characterize participants’ preferences for recontact and the factors driving their preferences. Methods: We developed a survey with a discrete choice experiment (DCE) to evaluate participants’ preferences for incidental sequencing results, including recontact. Semi-structured interviews in the pre-test of the DCE explored participants’ preferences for recontact. Interviews were analyzed using qualitative description. Results: We conducted interviews with 31 participants, 11 cancer and 20 public. Preferences were consistent between both groups. Participants responded favorably to being recontacted; many assumed that they would be recontacted with updates. While most participants considered updates to have personal and clinical utility, they would still be willing to receive initial results without future updates because they valued the genomic information. The few participants who did not want to be recontacted anticipated that updates would cause them anxiety. Many preferred updates delivered through a database. Participants’ prior negative healthcare experiences, such as their doctor not following up with their test results, led to a desire for “control” and access to updates via database. Participants who had more trust in their physician preferred clinician-involved delivery of updates. Participants also recognized feasibility challenges related to recontact, such as added burden to providers. Conclusion: Many, but not all, of our study participants assumed they would be recontacted with updated results and preferred to receive updates through accessing a database. Past healthcare experiences are important determinants of preferences for recontact. If confirmed, these findings could inform the development of strategies to optimize delivery of updated genomic results. Sponsors and Funding: Canadian Centre for Applied Research in Cancer Control (ARCC), St. Michael’s Hospital, The Keenan Research Summer Student Program.
A descriptive analysis of subway-related trauma at a Level 1 Trauma centre in Toronto, 2010-2018

Jordan Ho¹,², Muhammad Mansour³, David Gomez²,³,⁴

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Background: Over the past 10 years, the Toronto Transit Commission (TTC) subway system has continued to increase in ridership, and although the TTC has made improvements to safety, 131 subway incidents were reported between 2010 and 2016.¹ Management of subway-related trauma remains an under characterized area of injury.

Methods: We conducted a retrospective analysis of subway-related trauma at St. Michael’s Hospital (a Level 1 adult trauma centre) from January 2010 and December 2018. Data was collected and analyzed from the St. Michael’s Hospital Trauma Registry, including demographics, presentation at the emergency department (ED), details regarding management and stay, and outcomes.

Results: We found 51 cases of subway-related injury within 9 years. The average age was 41 years (SD 26), and two-thirds were male. 76% of cases were suicide attempts. Of 10 accidental cases, 8 were alcohol-related. 35% of patients presented with a severe GCS score (≤8), and 55% with a severe Injury Severity Score (≥15). The most common severe injuries (Abbreviated Injury Score ≥3) were head injuries, followed by thorax, lower, and upper extremities. Patterns of injury did not vary with intent. 25% of patients had a systolic blood pressure below 90 mmHg. 29% of patients had no severe injuries. 20% of patients presented to the ED deceased. Of those who survived the incident, average hospital length of stay was 20.9 ± 19.7 days, average ICU stay was 7.8 ± 7.9 days, and average duration of mechanical ventilation was 8.7 ± 10.3 days. 23.5% of patients required surgery and 50.9% of patients required ICU stay. Overall mortality was 29%.

Conclusions: Subway-related trauma patients present with severe injuries in multiple body areas. Most subway-related incidents are related to suicide attempts and alcohol use. With proper triage and management, the majority of patients survive. We recommend further research on injury patterns, alcohol usage, and demographics of subway-related trauma.
Experiences and Attitudes toward return to play following concussive injury in adult hockey players: implications for policy makers and injury prevention

S Pearce¹,4, S Zhang¹, K Boparai¹, M Cusimano¹,²,³

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Introduction: Despite evidence that repeated concussions pose a significant risk to long term health, especially when the injuries are close together, many adult hockey players return to play prior to recovering from concussion.

Objective: The following qualitative study was undertaken to determine the influence of social groups on professional hockey players during recovery from concussion. The study investigated if given reference groups pressured these players to prematurely return to play.

Methods: Semi-structured interviews with 17 ice hockey stakeholders (15 men and 3 women) including professional players, coaches, parents, and physicians were conducted over two years (2012-2014). These interviews were analyzed using thematic analysis according to Braun and Clarke⁵, under a symbolic interactionist lens.

Results: From this analysis, four primary themes centered around four social groups related to the player emerged. The first relates to the hockey “community”, particularly other players on the team, and their role as the primary social group for the hockey players. The players’ cognitions are often in accordance with hockey culture and, as such, feel great distress when they are removed from the team environment. The second theme is centered around league-associated social influences (ie. Coaches, owners, and trainers) who create and perpetuate a culture whereby players are punished for time spent out due to injury. The third theme depicts the nature of concussions and necessary recovery time as indicated by medical professionals as incongruent with the lifestyle and expectations of the athlete and reference others. The fourth theme describes how players act in accordance with what they believe to be the behavior of a typical “hockey player”, and pressure themselves to return to play quickly.

Conclusions and Implications for Practice: Understanding the factors that influence hockey players to return to play prior to full recovery from concussion has implications for both policy and treatment of athletes.

The inclusion of diabetes medicines on national essential medicine lists to improve health outcomes for diabetic patients

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Diabetes was the seventh leading cause of death in 2016, causing 1.6 million deaths worldwide(1). Many patients with diabetes are inadequately treated. Improving access to diabetes medicines may decrease the health burden from diabetes. Diabetes medicines on national essential medicines lists (NEMLS), which describe which medicines should be available in each country, vary considerably and the listing of such medicines on diabetes health outcomes are unknown(2). Our study examines the association between listing diabetes medicines on NEMLS with diabetes health outcomes, assessed by the health access and quality (HAQ) score for diabetes(3). We determined the number of diabetes medicines on NEMLS (n=137) and the number of medicines on NEMLS that overlap with the WHO model list(4). We used multiple linear regression to analyze the association between both the number of medicines on NEMLS and the number of medicines that overlap with the WHO model list with diabetes HAQ scores. In our secondary analysis, we determined medicines that were listed in many, but not all, countries (25%-75%) and used linear regression to assess the association between these medicines diabetes HAQ scores. Diabetes prevalence, mean expenditure per person with diabetes, and national GDP were controlled for in both analyses. Our crude analysis prior to controlling for covariates demonstrates a positive correlation between both the number of diabetes medicines on NEMLS, as well as the number of diabetes medicines on NEMLS that overlap with the WHO model list, with diabetes HAQ scores. Gliclazide, Glimepiride, and Glipizide were listed on 25% to 75% of NEMLS and their effectiveness on diabetes health outcomes will be analyzed. This project will quantify the health benefits associated with listing diabetes medicines on NEMLS and may identify the particular medicines that have the greatest impact on diabetes health outcomes.
The impact of policy on the percentage of open access articles funded by CIHR between 2008 and 2009: A systematic review

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Acknowledgements: The Keenan Research Summer Student Program

\textbf{INTRODUCTION:} Most federal agencies that disburse public funding for research mandate that publications be made open access (OA). In particular, the primary medical and health sciences research agency in Canada, Canadian Institute for Health Research (CIHR), mandated as of 2008 that all studies receiving funding from them in part or in full be published in open access (OA) journals. We aimed to determine the impact of this policy on CIHR funded studies published within one year of the mandate.

\textbf{METHODS:} We conducted a systematic search looking for articles that were funded by CIHR from January 1\textsuperscript{st}, 2008 to December 31\textsuperscript{st}, 2009 on Web of Science. To determine their status as OA or not, we cross-referenced them using Unpaywall, which is a not-for-profit organization that has a query tool for OA status lookup using digital object identifier (DOI). We analyzed the percentage of CIHR studies publishing in OA or not between the years 2008 and 2009 using Fisher’s exact test and odds ratio (OR).

\textbf{RESULTS:} We found a significant difference between the percentage of articles were published as OA or not between both years (P=0.011). Specifically, 50.2% of articles in 2008 were published as OA and 45.0% in 2009 were, with an OR of 1.23 (CI=1.05 to 1.44).

\textbf{CONCLUSION:} We found that there was a significant decrease in the amount of OA studies funded by CIHR after the 2008 mandate. Further research should be conducted to explore why this occurred, such as submission fees and journal impact factors.
Patient and prescriber experiences of a novel pharmacy model

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Sponsors and Funding: The Keenan Research Summer Student Program

Pharmacists dispensing medicines in Canada typically do not have access to medical records and medicine mailing is relatively uncommon in Canada. A pharmacy model which combines providing access to a short list of essential medicines, mailing medicines to participants and allowing the pharmacist access to patients’ electronic health record was implemented as part of a randomized controlled trial.(1) The purpose of this study was to evaluate the acceptability of the pharmacy model by patients and prescribers. We conducted qualitative studies of patients, prescribers and the pharmacist involved in the new pharmacy model. We found that patients were satisfied with the delivery service and said that their medicines arrived quickly and in good condition. Patients said that it was easy to obtain information about medicines and only 4% had unanswered questions. Prescribers said that it was helpful to allow the pharmacist to access patients’ electronic medical records and they welcomed the dialog with and suggestions made by the pharmacist. Overall, we found that a pharmacy model where medicines were mailed and the pharmacist accessed the electronic medical record was acceptable to patients and prescribers.
Reports of machine learning applications in several domains that involve utilizing structured or unstructured data have recently proliferated. Machine learning applications in medical imaging is one area which is continuing to get extensive attention from cross-disciplinary researchers and experts (medical experts, computer scientists, machine learning scientists) with the hope of providing improved patient care. Notably, certain diseases such as dementia and cancer, have received more attention from researchers as imaging is a part of the standard-of-care for those. However, pituitary tumors have received limited importance despite the role played by imaging in this disease. Therefore, in this work we reviewed the literature on machine learning applications in imaging analysis of pituitary tumors for the last 10 years. We grouped the studies by imaging type and analyzed the particular machine learning task, data inputs, reference standards, image pre-processing, methodology, and limitations. Of the 16 studies included in our analysis, 11 of the studies appeared in the last two years. Most of the studies utilized retrospective data, and followed a semi-automatic design machine learning pipeline. The studies included use of magnetic resonance imaging (MRI), facial photographs, surgical microscopic video, and spectrometry imaging. The objective of the studies covered 14 distinct tasks and majority of them addressed a binary classification problem. Only five of the studies had an external validation or a holdout set to test the performance of a final trained model. Through our concise evaluation and comparison of these studies, we highlight future directions so that potential ML applications using imaging can be developed and translated into a clinical benefit of pituitary tumor patients.

Keywords: Machine learning, medical imaging, pituitary, adenoma, tumor, image processing, MRI
Assessing Gaps in Evidence-Based Language and Formatting in Clinical Practice
Guideline Guidelines: An International Survey

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Background: Organizations around the world produce clinical practice guidelines at an astonishing pace, with great effort and at substantial cost. However, despite broad dissemination efforts, large gaps remain between guideline recommendations and real-world practice across health systems, practitioner and patient types, and diseases. It is becoming increasingly clear that certain features, such as the language used and formatting of the guideline itself may influence its uptake. Our aim is to investigate guideline developers’ perceived needs for support in optimizing language and formatting according to best evidence.

Methods: We will invite (by e-mail) the corresponding authors from guidelines registered in the Guidelines International Network guideline database in the last 5 years (~1000 guidelines) to complete an online cross-sectional survey. The survey will use radio buttons, tick boxes, open text fields, and Likert scales to investigate: 1) which tools authors currently use in guideline development; 2) authors’ perceptions of these existing tools with regards to guidance on language and format; and 3) authors’ priority rankings of various language and format constructs that have been reported in the literature.

Analysis: We will report quantitative descriptive statistics of the respondents’ demographics, existing guideline tool usage patterns, perceptions regarding existing tools, and priorities. We will also summarize free-text entries qualitatively.

Discussion: The proposed survey will allow us to identify gaps in existing guideline development tools and will guide development of a tool specifically aimed at improving the language and format of guidelines with a view to optimizing their implementability.

Funding: The Keenan Research Summer Student Program
Applying Implementation Science to build IPV screening and referral capacity in a Fracture Clinic: Lessons learned from a pilot study

Jessica J. Rodrigues1,2, Patricia O’Campo1,3, Alisa J. Velonis4, Jeremy Hall5,6, Milena R. Vicente5, Ines DeCampos7, Lori Lamando7, Mari Vella7, Esther Carter7, Pearl Buhariwala1, Janisha Kamalanathan1, and Maha Hassan1

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Background: Between 25-50% of women in Canada will experience physical, sexual and/or psychological violence from an intimate partner. At the St. Michael’s Hospital Fracture Clinic, 1 in 4 women reported experiencing intimate partner violence (IPV) within a year of their fracture. Building upon the need for and motivation to support a comprehensive screening and referral initiative, a team of researchers and clinicians used methods of implementation science to strengthen existing screening activities in the clinic. Methods: The Applied Implementation Framework was adapted from the National Implementation Research Network to guide data collection across the four implementation stages. A technology-enhanced IPV screening program (https://withwomen.ca) was developed and piloted in three Fracture Clinics during May and July of 2019. Analysis focused on understanding the clinic’s capacity for change, strengths and weaknesses of IPV screening in the clinic, resources needed for screening, and pilot data used to inform practice and scale-up of the program. Results: The process revealed key strengths and challenges within existing clinic structures and screening practices that were not immediately obvious to either the research or clinical teams. The use of technology helped overcome the limitations of traditional screening. Pilot data reported conservative IPV screening rates of 94%, 93%, and 71% across the three clinics, with patients demonstrating overall acceptance of the screening process. Discussion: Implementation science offers proven strategies to overcome implementation barriers so that individuals can receive the full benefits of evidence-based programs such as routine IPV screening. Successful adaptation and uptake of a rigorous IPV screening program in the Fracture Clinic has led to increased access to screening, information, and referrals for all female patients. Funding Agencies: St. Michael’s Hospital Foundation.
Associations of medicines on national essential medicines lists with health outcomes in 137 countries

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Medicines are supposed to improve health outcomes, so countries with better medicine availability should have better health outcomes when controlling for other factors. Given that countries use lists of essential medicines to determine which medicines are available and publicly funded in healthcare institutions, the listing of these medicines may indicate the effect of medicines on population health. Using a database of national essential medicine lists (NEML, n=2068) and a national index of health access and quality (HAQ, n=137), we hypothesize that listing a medicine on an NEML is associated with an increase in the mean of the HAQ index, which is an indicator of health outcomes in conditions amenable to medical care (1–3). Using multiple linear regression for 2068 medicines, adjusted for 3 covariates: log-population, log-health expenditure per capita, and log-population size, we will assess for associations between medicines and indices of population health amenable to medical intervention. We also seek to conduct both lasso and ridge regression using all 2068 medicines and the above 3 covariates to select for medicines that most significantly contribute to HAQ index variation. We will use simulation to determine the likelihood that observed observations are due to chance. A review of the literature will be completed on the clinical effectiveness of medicines that are associated with health outcomes to assess the credibility of putative associations between medicines and HAQ index. Secondary analyses seek to assess variation in country listing of medicines on NEMLs through clustering algorithms such as principal component analysis and latent discriminant analysis. This study may identify medicines that are associated with better population health outcomes, and these medicines could be adopted more broadly by countries.

Sponsors and Funding: The Keenan Research Summer Student Program
Background: Most HIV prevention programs targeting sex work focus on female sex workers (FSW), and little is known about the epidemiology of HIV and sexual behavior among clients and non-paying male sex partners of FSW. We sought to estimate the HIV prevalence, number and types of sexual partnerships among male sex partners of FSW in Sub-Saharan Africa.

Methods: We searched five electronic databases (Medline, EMBASE, The Cochrane Database, Scopus, CINAHL) and six grey literature sources for articles reporting HIV prevalence or sexual partnerships of clients and non-paying male partners of FSW published between January 2004 and October 2018. HIV prevalence estimates were pooled using a random effects model to obtain overall and regional HIV prevalence among clients in Sub-Saharan Africa. Subgroup analyses investigated the geographical heterogeneity in HIV prevalence among clients in East, West/Central, and Southern Africa.

Results: The search identified 4,634 articles, of which 102 studies met the inclusion criteria. Zero articles contained data on non-paying partners of FSW. Fifty-three studies, representing 11,772 clients of FSW across 36 countries in Sub-Saharan Africa, were included in the pooled HIV prevalence estimate. Overall, HIV prevalence among clients was 7.0% (95% CI: 5.5-8.8%). HIV prevalence among clients in West/Central Africa was 3.9% (2.2-6.6%, I²=91.6%, n=27 studies); in East Africa was 8.6% (6.6-11.1%, I²=79.3%, n=15); and in Southern Africa was 15.5% (12.4-19.1%, I²=76.3%, n=11). Five studies, representing 1,811 clients, reported the number and types of sexual partnerships of clients. The median number of FSW partners per client (n=2) ranged from 1-5. The proportion of clients with a spouse/common law partner (n=3) ranged from 6.8-22.8%.

Conclusion: The high prevalence of HIV in clients of FSW in Sub-Saharan Africa suggests a need for HIV prevention programming focused on and tailored to clients. Future research on the epidemiology of HIV among non-paying male partners of FSW is also needed.
A Glimpse into the Far-Reaching Implications of Organizational Policies on Workplace Incivility Amongst Staff in Acute Care Facilities: a Literature Review

Natalie Chen 1, Taylor Kumer 1, Teresa J. Valenzano 2, Jane Topolovec-Vranic 2

1. The Keenan Research Summer Student Program, Li Ka Shing Knowledge Institute, Toronto, Ontario
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Workplace incivility is defined as rude or discourteous behaviour exhibited by staff or visitors that is targeted at an individual in a corporate setting. It is an unfortunate yet common phenomenon among healthcare professionals and typically appears through the use of condescending tones, exhibiting demeaning body language or spreading negative beliefs about a coworker. In addition to creating a stressful work environment, incivility between staff may result in a decrease in work performance and implicate patient care. Specifically, it may decrease the quality and frequency of patient-staff communication, prolong hospital stays and result in higher rates of medication errors. To understand how incivility is fostered, we will conduct a systematic review to determine the impacts that different organizational factors may have on certain workplace environments and to identify solutions that can be used to promote civility. A comprehensive multi-engine literature search will be conducted and satisfactory articles will be reviewed for their study quality and level of evidence. Data will then be extracted from the remaining articles to understand how organizational policies can mitigate workplace incivility and encourage collaborative interprofessional behaviour - both of which can offer tangible benefits toward employee satisfaction and hospital productivity.
Systematic review of the impact of chronic tetracycline class antibiotics on antimicrobial resistance in host normal flora

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I had the wonderful opportunity to work in Dr. Darrell Tan’s HIV and STI Prevention and Management Lab, focusing on clinical trials for HIV and STI interventions. With newly improved HIV treatments and HIV PrEP, many clinical studies have shown possible efficacy in using doxycycline as STI PrEP to prevent syphilis and chlamydia. However, as antimicrobial resistance (AMR) rises globally, especially in developed countries, interventions such as doxycycline, should be better managed to not feed into this public health issue. Thus, my project was to perform a systematic review on the chronic impact of tetracycline class antibiotics on AMR. We used MEDLINE and EMBASE to independently screen and include articles relevant to our topic with the help of a second reviewer. Afterwards, we extracted the data onto data extraction forms where we could more easily analyze current AMR trends. Currently, we are in the stage in analyzing the data and writing the manuscript.

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Optimal Management of Emergency General Surgery Patients – Creating a Worldwide Registry of Traumatic and Non-Traumatic Surgical Emergencies (WIRES Project)

O’Neill, Melissa¹; Rezende-Neto, Joao²; Coccolini, Federico³

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² Division of General Surgery, St. Michaels Hospital, Toronto, Canada
³ Department of General, Emergency and Trauma Surgery, Bufalini Hospital, Cesena, Italy

BACKGROUND: Due to the uniqueness of acute surgical conditions and the high morbidity and mortality rates associated with them, optimal management of Emergency General Surgery (EGS) patients represents one of the most significant globally-faced health challenges. To improve the management of these cases, the WIRES project (WSES International Registry of Emergency General Surgery) has been initiated to allow surgeons to register their activity and to access a worldwide register of surgical emergencies.

METHODS: This is a prospective, observational, multicentre study aiming to enroll patients requiring evaluation and management by an emergency surgeon between September 2018 and September 2028. The objective of this study is to evaluate and stratify the environment, indications, treatments and outcomes of varying acute surgical conditions requiring operative or non-operative management.

EXPECTED OUTCOMES: There has been a slow but progressive improvement in the operative and non-operative management of EGS cases. With access to the benchmark values in the registry, differences in morbidity and mortality rates linked to a range of techniques, environments and variables can be evaluated. Since several variables may influence treatment efficacy and patient outcomes, we anticipate that having access to this registry will allow physicians and other healthcare professionals to refine treatment and in turn, improve patient outcomes.

CONCLUSION: We anticipate that creating an international registry of surgical emergencies will improve operative and non-operative treatment outcomes of EGS patients by providing surgeons with benchmark values linked to the management of varying acute surgical conditions.
Impact of Augmented Reality on Procedural Skills Acquisition in a Simulation-Based Training Curriculum for Polypectomy: A Pilot Study

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Introduction/Background: Augmented reality (AR) involves the superimposition of a computer-generated video on a user’s view of the real world to enhance perception of reality. Learning in colonoscopy, a procedure for detection and removal of pre-malignant polyps, may be improved by AR, as polyps may be detected ad hoc. AR could allow for learning to occur at the time of polyp detection. This study’s objective is to assess the impact of AR in a simulation-based training (SBT) curriculum for novice endoscopists learning colonoscopy. Methods: We conducted a parallel group, randomized controlled pilot study. 22 novice endoscopists (<25 procedures) were randomized to a standard (N=11) or AR curriculum (N=10). All participants received 5 hours of simulation training using the EndoVRⓇ virtual reality (VR) simulator (CAE Healthcare, Montreal). Participants using AR curriculum had an instructional video on polypectomy, triggered upon encountering a polyp during VR colonoscopy cases. Multiple videos were used to progressively introduce polypectomy techniques of increasing complexity. Trainees were tested after training using: standardized patient (SP) scenario utilizing live actors with EndoVR simulation; and a transfer test using the Koken mechanical simulator (KOKEN CO., Tokyo), which simulated polypectomy. The primary outcome was to assess polypectomy skills evaluated by experts using the Direct Observation of Polypectomy Skills (DOPyS) score, an assessment tool with good validity evidence. The secondary outcome was to measure intrinsic, extrinsic and germane cognitive load experienced by endoscopists using scores from the self-assessed Cognitive Load Index for Colonoscopy (CLIC). Results: Differences in DOPyS scores during SP scenarios and Koken transfer tests were not significant between the AR and standard curriculum groups during all 3 testing phases (pre-test, post-test and delayed-test). During the SP delayed-test and Koken delayed-test, the AR group experienced significantly lower levels of intrinsic cognitive load/CLIC scores (1.7 ± 0.40 and 1.4 ± 0.47 respectively) compared to the standard curriculum group (3.3 ± 0.38 and 2.9 ± 0.45 respectively) (P=0.01 and P=0.03 for differences between respective intrinsic CLIC scores). Conclusion: Augmented reality is a promising novel technique in polypectomy training for novice gastroenterologists. The results strongly suggest that AR allows novices to perform endoscopic procedures post-training with less mental strain and cognitive load than those trained using conventional methods. Completion of this randomized trial is required to evaluate the clinical impact of an AR intervention on procedural learning.

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Tumour micro-ecosystems may modulate glioblastoma chemoresistance

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Resistance to chemotherapy in glioblastoma (GBM), the most frequent adult brain tumor is inevitable, rendering the disease invariably fatal. Recent studies have associated chemoresistance with the range of cells that compose the tumor micro-ecosystem (TME), particularly immune cells. In the current study, machine learning technologies were leveraged to analyze open genetic data repositories and screen 22 immune cell fractions for correlation with tumour chemoresistance in 417 GBM samples from The Cancer Genome Atlas. Based on distinct clustering of immune cells, four GBM tumour subgroups with differing chemoresistance profiles were identified. These subgroups had very little overlap with current transcriptomics-based categories. Some of the subgroup specific mechanisms were overlapping while others were distinct between clusters. Clusters with a higher fraction of macrophages (M0, M1, M2), CD4 T cells and activated mast cells were suggestive of a pro-tumor environment, wherein Wnt signalling or Ubl conjugation pathways may modulate chemoresistance. Contrastingly, clusters more enriched in monocytes and gamma-delta T cells show a suppressed immune microenvironment where chemoresistance may be associated with the complement pathway or IgG isotype switching. These results suggest a classification for GBM based on immune cell fractions of the TME in addition to the existing transcriptomics-based scheme. This classification seems to better capture differences in GBM chemoresistance and sheds light on diverse and multicellular processes. The findings may also have implications on targeting the tumour micro-ecosystem to enhance oncotoxic effects of chemotherapy in this incurable disease.

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A Single Centre, Retrospective Analysis of Joint Function and Clinical Outcomes on Patients with Hemophilia A or B undergoing Total Knee Arthroplasty.

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BACKGROUND & RATIONALE: Hemophilia A and B are X-linked recessive bleeding disorders on the basis of coagulation factor VIII and factor IX deficiency, respectively. Approximately 3,700 Canadians are affected by either hemophilia A or B. One common feature of hemophilia is hemarthrosis, which is characterized by recurrent bleeding into joints. Blood within the joint space has detrimental effects and leads to the development of hemophilic arthropathy which significantly impacts quality of life in these patients. Patients with hemophilia are prone to end-stage joint disease resulting in the need for total joint arthroplasty, with total knee arthroplasty being particularly common in our clinical setting. Orthopedic surgeries in hemophilia patients are particularly challenging due to high rates of complications including infection, fractures, venous thromboembolism and major bleeding. Additionally, these patients will continue to be at risk for musculoskeletal bleeding into these target joints following surgery. We wish to compare functional knee status pre- and post-operatively in this patient population to better understand the impact on patient quality of life.

OBJECTIVE: To compare the functional status and quality of life and clinical outcomes after a total knee arthroplasty is performed on a patient with moderate to severe hemophilia A or B, as measured by the Oxford knee score and the EQ-5D questionnaires at baseline and 6 weeks post-operatively.

METHODS: We propose a retrospective review of all knee arthroplasties in hemophilia patients performed at St. Michael’s Hospital from 2017 to 2019. We will capture demographic information and information related to their hemophilia and treatment regimen. Functional status will be determined using the orthopedic Oxford knee score, captured

FUTURE STEPS: We will work to secure REB approval, followed by data collection.
Perioperative Symptom Burden and Quality of Life in Patients with Cushing’s Disease Treated with Endoscopic Transsphenoidal Surgery

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Introduction: Cushing’s disease (CD) is a rare endocrine disorder arising from hypercortisolism caused by a corticotropin-secreting pituitary adenoma. Prolonged exposure to hypercortisolism is associated with a range of generic and disease-specific symptomatology and comorbidities. The burden of illness elicits impairments in patient’s quality of life (QOL).

Methodology: Patients with confirmed CD were evaluated before and after endoscopic transsphenoidal surgery (ETSS) using a patient-report checklist of symptoms and three validated QOL measures. All CD patients were biochemically-cured as assessed using Endocrine Society criteria. A group of patients with non-functioning pituitary adenomas (NFPA) were recruited as controls and assessed before and after ETSS. We then analyzed: 1) Changes in symptoms and QOL within CD and NFPA groups across all timepoints before and after ETSS; 2) Differences in symptoms and QOL between CD and NFPA at each timepoint before and after ETSS.

Results: A greater symptom burden was observed relative to NFPA before and after ETSS, particularly in the dermatologic, cognitive, neurologic, psychiatric, and non-specific domains. ETSS had little effect on CD patients and most symptoms persist after ETSS despite biochemical cure. In CD patients, an overall statistically significant impairment in QOL was observed before and after ETSS compared to NFPA across all measures. In general, QOL deteriorates leading up to ETSS. QOL improves slightly after ETSS in general health perceptions, physical functioning, and limitations due to emotional health, but remain stagnant in other domains. During remission, QOL remains impaired, but continues to improve toward baseline levels.

Conclusion: Symptom and QOL in CD has been demonstrated to be impaired relative to NFPA overall, which corresponds with existing literature. The progression and domains with the greatest impairment were identified, and were demonstrated to improve towards baseline. Observed impairments highlight need for additional physical and psychological resources, such as directed patient education or support groups.

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The effectiveness and stakeholder satisfaction of the use Telemedicine Videoconferencing for patients undergoing Bariatric Surgery at St. Michael’s Hospital

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Obesity is a major population health issue in Canada, affecting about one in five Canadian adults.¹ It increases both the risk of other chronic health conditions—such as type 2 diabetes, high blood pressure and sleep apnea—and the use of health resources.²–⁶ Many interventions can help individuals with obesity lose weight. These include lifestyle changes (diet modifications and increased physical activity), medical counselling and bariatric surgery. Evidence shows that bariatric surgery can be an effective tool for significant weight loss among people who have severe obesity, in turn leading to improvements in their health status and quality of life.⁴, ⁷–⁹ Telemedicine, which is the use of videoconferencing technology to deliver patient care over a distance, bridges the gaps between patients and physicians. We assess the effectiveness of Telemedicine videoconferencing for preoperative surgical and anesthesia assessment in identifying medical issues that required further tests prior to surgery. Furthermore, we investigate the frequency of surgery cancellations as well as satisfaction amongst patients, surgeons, and anesthesiologists with the approach.

Comparison of overall survival in adult glioblastoma patients undergoing circumferential resection versus internal resection: a single institution retrospective study

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Keenan Research Summer Student Program

Background: Glioblastoma (GBM) is a primary brain malignancy with a poor prognosis. Surgical resection is the mainstay of therapy with the goal of achieving maximal safe resection, which has been proven to improve quality of life after diagnosis (Lacroix et al., 2001). A standard technical approach to GBM resection involves entering the tumor directly and resecting from within. An alternative approach to ensure maximal resection involves performing a circumferential resection of the tumour. Purpose and significance of research: In this retrospective matched cohort study, we will compare the morbidity and mortality outcomes of patients who have undergone either internal or circumferential resections. Results from this study could help determine whether circumferential resection is a more optimal technique for achieving maximal safe resection and improving overall patient survival, without creating any new deficits. Methods and Discussion: Seventy GBM patients have been collected. GBM patients having circumferential surgeries (n=27) from 2007-2018 at St. Michael’s Hospital were used to form the cases. These cases were matched with GBM internal resection patients based on age (within ten years), Karnofsky Performance Scale (KPS), pre-operative tumour size, sex, and tumour lobe location. Forty-eight matched internal patients were included. The primary outcome measure is overall survival from the date of surgery, confirmed by records from the Ontario Death Registry. The secondary outcome measure of extent of resection (EOR) is determined based on postoperative contrast imaging analysis by neuroradiologists as either gross total (GTR) or subtotal resection (STR). We found that the circumferential technique significantly increases the ability to achieve GTR (p=0.00067). Other secondary outcome measures are post-operative neurological deficits before discharge, operative blood loss, and length of hospital stay which are not significantly different between treatments (p>0.25). Wilcoxon-rank sum and chi-square tests were conducted to analyze the differences between the groups for the secondary outcomes. After data collection, we will conduct a survival analysis using the log-rank test, to analyze the primary outcome measure in both treatment groups.
INTRODUCTION: The rate of aging worldwide is much greater than it has been in the past. Accordingly, the average surgical patient is becoming older and more frail. Older patients undergoing surgery are at increased risk of adverse post-operative outcomes compared to younger patients. There is increasing evidence that structured perioperative geriatric care programs have positive effects on the outcomes of elderly patients. Despite this, there is little published data regarding what models of perioperative geriatric care are delivered in Canada. It will be important to survey and evaluate whether structured perioperative geriatric programs exist in hospitals across Canada, and the components of these programs. This environmental scan will provide data on the current landscape of perioperative geriatrics in Canada.

METHODS: We developed a preliminary web-based survey to evaluate the existence of perioperative geriatric care models and how these services are delivered. Survey content was based on best practice guidelines from the American Geriatrics Society and American College of Surgeons and a pre-existing survey for perioperative geriatric care from the United Kingdom. To evaluate comprehensiveness, clarity, reliability and validity of the survey, it will be sent for review by a group of physicians in surgery, anesthesiology and geriatric medicine who are experts in the field of perioperative geriatrics. The survey will be finalized based on revisions made by these group of respondents. Pilot testing will also assess test-retest reliability. Final participants of the survey will be identified through departmental leads at each university hospital for surgery, anesthesiology, and geriatric medicine.

EXPECTED RESULTS: We expect the data collected from this survey to demonstrate a variety of different models of perioperative geriatric care. This will serve as a foundation for future development of standard best practices and contribute to the development of a national strategy on improving clinical outcomes of geriatric surgical patients.
Introducing a new EEG based index for monitoring recall under sedation

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Awareness under general anesthesia, and the later recall of the events of surgery, is a dreadful complication which can leave lasting mental trauma behind such as post-traumatic stress disorder, anxiety, and depression (1). Various EEG-based technologies (such as BIS) were developed in order to identify this condition during anesthesia, using an EEG sticker on the forehead measuring the frontal EEG activity (2). However, these monitors are inaccurate due to lack of sensitivity to various hypnotic agents (3) as well as sensitivity to muscle activity, which may falsely report anesthesia in awake patients (4). We have developed the posterior/anterior (P/A) index (in the range of 0-100) for assessing recall after anesthesia. The aim of this prospective study is to assess whether this index would relate to recall of awareness in sedation. We hypothesize that the P/A index would accurately predict recall after sedation, whereas a prefrontal based electrophysiological method (BIS) would not relate to recall. Ethics approval for this prospective observational study has been obtained (REB 18-308). Preliminary results from our pilot study demonstrated that the P/A index differentiated between patients with recall (MD+R) (median 66.75, IQR 53-78) and no recall (MD-R) (median 27.5 IQR 15.5-50, p=0.006). However, BIS could not separate between [MD+R] (median 83.5 IQR 81.5-84) and [MD-R] (median 83.5 IQR 81.5-84, p=0.348). The P/A index was not influenced by EMG (R²= 0.009, p=0.69) whereas the BIS was influenced by EMG (R²=0.311, p=0.013). The aim of the current trial is to repeat the results of the previous study with an improved EEG system, and to assess whether this index would relate to recall of awareness in sedation at a high temporal resolution.
Mathematical Modeling of antibiotic-resistant organisms (ARO) transmission in health-care facilities: a systematic review of methods and parameters

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Background: The increasing prevalence of health-care associated infections due to antibiotic resistant organisms (AROs) is a global health burden. There are various interventions targeted towards mitigating ARO transmission. However, the efficacy of these interventions are challenging to investigate due to ethical and resource constraints. Mathematical models are increasingly being applied to understand ARO transmission dynamics in healthcare settings. We propose a systematic review of mathematical models to (1) determine the range of parameter estimates and model structures used in ARO transmission modelling within healthcare facilities and (2) to elucidate the mechanisms by which heterogenous parameter estimates and model structures lead to variability in model outcomes.

Methods: MEDLINE, EMBASE, and Scopus will be searched for studies that describe mathematical models of ARO transmission dynamics within a hospital or long term care facility. Study screening will be done by two independent reviewers with disagreements resolved by a third reviewer. Bias will be assessed using a checklist devised specifically to assess the quality of mathematical models of transmission dynamics. The results will be narratively synthesized to describe the variability of parameter estimates, model structures, and AROs modelled. A quantitative synthesis of the results will also be performed to investigate outcome heterogeneity of different parameters and models using one-way sensitivity analyses and partial rank correlation coefficients.

Discussion: This review will identify gaps in the area of mathematical modelling of ARO transmission dynamics and identify specific AROs and interventions that require further study. It will also provide insight on how the selection of parameter estimates and model structures influence model outcomes. Our results will help interpret current ARO models and assist future modellers in selecting the optimal model parameters and model structures for evaluating ARO transmission in healthcare settings.

Study registration: Our protocol is registered in the PROSPERO database (registration number:CRD42019132705).
REM rebound predicts CPAP compliance in patients with obstructive sleep apnea

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BACKGROUND: Factors that predict CPAP compliance remain poorly understood. It has been suggested that the presence of improved sleep architecture during CPAP titration polysomnography may predict better long-term CPAP compliance. We sought to determine whether the presence of REM rebound during the CPAP titration study would predict improved CPAP compliance in a group of patients newly diagnosed and treated for obstructive sleep apnea.

METHODS: The study was conducted at the sleep clinic of St. Michael’s Hospital, a large urban academic hospital in Toronto, Canada. 100 patients who underwent both an initial diagnostic sleep study and a second CPAP titration study were included. Patients with prior exposure to CPAP or who did not return for follow-up visits with downloaded data from either a loaner or purchased CPAP machine were excluded from the study. Sleep architecture was compared between the two studies and REM rebound was defined as an absolute increase of 10% between percentage of total sleep time comprised of REM sleep (%REM) on the night of CPAP titration compared to the baseline diagnostic study. Compliance measures were obtained from downloaded information from CPAP machines during a follow-up clinic visit.

RESULTS: Patients were 55% male and 45% female and had mostly severe OSA (average AHI 50.9 ± 23, 1% mild, 19% moderate, 81% severe). The average age was 55.2 ± 13.4 years and patients were generally symptomatic from excessive daytime sleepiness (ESS 9.2 ± 5.1) Patients who manifested REM rebound during their CPAP titration study were found to have greater compliance with CPAP at the time of their follow-up visit than those without REM rebound (91.5% vs 67%, respectively, of days used > 4 hours, P = 0.021).

CONCLUSIONS: The presence of REM rebound during an initial CPAP titration study predicts improved compliance with CPAP.

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Tacrolimus Intra-patient Variability as a Measure of Medication Adherence

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Non-adherence to immunosuppressive therapies after kidney transplantation has been attributed to a high blood drug level intra-patient variability (IPV), graft loss, de novo donor-specific antibodies, and rejection. The present retrospective study aimed to determine the utility of tacrolimus IPV in detecting non-adherence by examining the relationship between self-reported adherence and tacrolimus coefficient of variability (COV), a surrogate for IPV. The impact of sociodemographic factors, e.g. current age, age at transplant, gender, ethnicity, language, socioeconomic status, previous transplants, transplant type, drug formulation and formulation change number on COV were also assessed. In addition, the change in COV over time was examined. Patients included were 1-year post kidney transplant as of March 31st, 2019, prescribed tacrolimus as an immunosuppressant and had a self-reported adherence status. A total of 599 unique patient files were assessed. Predicted outcomes include a significant correlation between COV and self-reported adherence, with a higher tacrolimus COV correlating with decreased age at transplant, non-English speakers, lower socioeconomic status, more males than females, longer time since transplantation and having received a live donor kidney. Since tacrolimus COV testing occurs concurrently with routine blood work, this inexpensive method may be able to identify non-adherent patients that can inform physician intervention to prevent adverse outcomes.
Pituitary tumours have the potential to compress the optic chiasm and cranial nerves III, IV, and VI, which can result in various visual deficits in patients, such as decreased visual acuity, visual field defects and optic disc atrophy. Problems with eyesight have a significant impact on an individual’s quality of life (QOL), as it can leave them unable to perform daily tasks such as cooking for themselves and driving, and the testing and treating of visual deficits can lead to financial strain for the patient. Presently, there are no specific instruments aimed at assessing vision-related QOL in pituitary tumours. The development of a vision related QOL questionnaire for those impacted by a pituitary tumour could allow for the burden placed on patients going through continuous ophthalmologic testing to be reduced and provide a preliminary assessment on the impact on QOL due to the changes in vision. The objective of this study is to develop a disease-specific, vision-related QOL questionnaire that could act as a simpler and more economic preliminary test to track the progression of visual impairment in patients with pituitary tumors. We implemented a questionnaire development methodology, consisting of item generation and item reduction. A patient-centered approach was utilized, where the patients recruited in this study were diagnosed with a pituitary adenoma. Interviews with 44 patients were coded and a literature review was conducted to develop a preliminary list of 152 items, categorized into 6 domains including visual symptoms, barriers to care, and support network. The list of items was reviewed by experts (e.g. neurosurgeon, neuro-ophthalmologist), resulting in a list of 114 items to be distributed to patients. Through the initiation of the item reduction phase, we aim to develop a concise, clinically relevant QOL questionnaire that could facilitate clinical and research efforts with pituitary tumour patients.
Spinal cord stimulation (SCS) has proven to be a clinically and socioeconomically effective alternative for patients with chronic pain, and who are resistant to pharmacological and less invasive interventional treatments (1). SCS is a safe approach for patients with clinical indications including chronic intractable neuropathic pain, failed back surgery syndrome, and complex regional pain syndrome (2). In addition to the primary objective of decreasing pain intensity, patient-oriented outcomes such as enhanced physical activity, resumed employment, and reduced health care expenditures must be considered. A Neuromodulation service has recently been established at St. Michael’s Hospital. It is an outpatient-based service in two stages: 1) a trial period of SCS implantation with external battery, where success is defined as at least 50% reduction of pain intensity or improvement in the functional status; and 2) permanent internal pulse generator implantation. This aim of this retrospective study is to determine the degree of pain relief (Numerical Rating Scale), changes in narcotic dosing, activity levels, disability (Oswestry Disability Index), and return to work, when appropriate. We hypothesize that patients after having been implanted with a spinal cord stimulator will experience less pain and therefore will require less medication, have increased activity and resume employment. The preliminary results include a conversion rate from phase 1 to 2 of 93%, notably higher than a 70% conversion rate measured by American institutions (3). An average pain reduction of 71% was measured. Increased physical activity levels were reported by 74% of the patients. Reduced opioid usage was observed in majority of patients, with 46% of patients completely weaned off. This result is a great achievement not only from a financial point of view but also for the patients as they avoid the known detrimental consequences of the opioids.

1) Rosenberg Pain Med 2016
2) Van Buyten Neuromodulation 2017
3) Huang Neuromodulation 2014
Reverse Triggering, A Missed Phenomenon

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IMPORTANCE: Reverse triggering (RT)1 is a type of asynchrony defined by the presence of patient’s inspiratory effort triggered by the ventilator. Asynchronies are associated with prolonged mechanical ventilation (MV), longer hospital stay, and increased mortality. RT in particular might be injurious for the lung and the diaphragm. RT is detected through flow, airway pressure (Paw) and esophageal pressure (Peso) or electrical activity of the diaphragm (EAdi) tracings. Diagnosis can be challenging and, despite being a frequent phenomenon, is usually missed at the bedside.

OBJECTIVES: A systematic review of published papers that contain tracings to determine the presence of RT that were missed.

METHODS: Medline and EMBASE databases were searched utilizing key words related to asynchrony and MV. Included manuscripts were those containing respiratory waveforms (Paw, flow with or without Peso or EAdi). Excluded manuscripts were studies involving animal, non-invasive ventilation, high frequency oscillation, cardiac synchronization, toracho-abdominal synchrony, negative pressure ventilation and spontaneous modes of ventilation. Each tracing from included manuscripts was analyzed for the presence of RT (definite or possible) using predefined criteria by two experts and assessing if it was missed by the original authors.

RESULTS: 2479 citations were screened; 976 manuscripts were eligible for full-text screening. So far, 679 full text articles were retrieved, 487 manuscripts have been excluded for the lack of appropriate tracings and 192 manuscripts have been included for the final analysis. From this, 644 figures have been classified of which, 64 (9.9%) figures accounted for possible (n=16) or definite (n=48) RT. 60 (93%) were not correctly described as being RT.

CONCLUSIONS: Preliminary results indicate that reverse triggering is a frequent phenomenon and has been missed in previously published papers.

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Investigating The Use of Transcutaneous Bilirubin Measurements on Neonates With Unexposed Areas of Skin To Phototherapy

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BACKGROUND: Transcutaneous bilirubin measurements (TCB) are currently used as a screening tool prior to phototherapy to determine at-risk infants for hyperbilirubinemia. Once a baby undergoes phototherapy, or exceeds the threshold for treatment, only blood samples measuring total serum bilirubin (TSB) are used to monitor hyperbilirubinemia. When an infant is under phototherapy TSB is measured every 6-12 hours, which endues much stress and pain on the neonate. The use of TCB after phototherapy commences would be beneficial – however most studies have reported deceased effectiveness as a result of exposed skin under phototherapy. Only some pilot studies have studied the effectiveness of TCB on unexposed areas to phototherapy by covering the skin. These are limited to small sample sizes.

METHODS: A prospective cohort study of neonates > 35 weeks receiving phototherapy at St. Michael’s Hospital. At the time of each clinically required TSB, two TCBs will be completed within 15 minutes. The TCBs will be recorded on exposed and unexposed areas of the forehead during phototherapy. Once a neonate starts phototherapy a 3M RedDot electrode will be used to cover a part of the forehead during phototherapy. To determine the impact of covering the skin during phototherapy, agreement and correlation coefficients, as well as Bland-Altman Plotting, between TCB and TSB will be completed.

RESULTS: 129 TCB measurements have been conducted on neonates > 35 weeks gestation on exposed areas of skin to phototherapy resulted in a mean difference of -16.9 umol/L (-25.7 to -8.1). To determine the effects of covering the skin, 200 term infants undergoing phototherapy will be recruited and TCB values on covered areas of skin will be evaluated at the time of a TSB.

CONCLUSION: Covering the skin may offer a new approach to using TCB after phototherapy.
Title of Project: Investigating structural brain changes following mild Traumatic Brain Injury using advanced Magnetic Resonance Imaging

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Mild Traumatic Brain Injuries (mTBIs) may be associated in some cases with serious symptoms and relatively long recovery periods. However, conventional radiological exams used to assess concussed individuals generally yield negative results and thus provide negligible insight into the prognosis of mTBI patients. As such, the present research aims to use advanced Magnetic Resonance Imaging (MRI) techniques to identify markers in the early stages of injury that correlate with clinical outcomes through analyzing the brain images of previously concussed individuals at different time points, as well as those of their healthy control counterparts. These advanced MRI techniques will be used to specifically probe the association of mTBIs to microhemorrhages, extracellular edema, and subtle changes in neuroanatomy. In this way, not only does this investigation have the potential to aid in the creation of a more profound understanding of the manifestation of mTBIs, but it may also support the development of more targeted and efficacious methods for rehabilitation.

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A multi-centred stepped wedge cluster RCT of the de-adoption of oral chlorhexidine prophylaxis and implementation of an oral care bundle for ventilated critically ill patients

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Critically ill patients placed on ventilation are susceptible to ventilatory-associated pneumonia (VAP), the most commonly acquired intensive care unit (ICU) infection. To combat VAP, oral care “bundles” are distributed to ventilated patients as prophylaxis. Oral chlorhexidine, a mouthwash incorporated into a routine oral care bundle, is supported by the literature in its ability to prevent VAP; however, recent studies surrounding the clinical use of oral chlorhexidine report complications such as dry mouth, stomatitis, and bad taste, and most importantly, a statistically significant increase in the mortality of patients receiving oral chlorhexidine bundles. Therefore, we are conducting a multi-centred, stepped wedge cluster randomized control trial to determine whether reductions in mortality, VAP, and improvements in oral health will occur following the de-adoption of oral chlorhexidine for substitution with an alternative, evidence-based oral care bundle in ventilated patients. The procedures for altering oral care practices in the clinic can be evaluated and compared between ICUs, as six are participating in the study. Additionally, our study leverages an existing clinical registry, iCORE, that has been collecting relevant data on ventilated, ICU patients for the past three years, which we will use to derive pre- and post-intervention VAP rates and ICU mortality. By investigating the detriments of oral chlorhexidine administration, our study can pave the way towards optimal oral hygiene and hospital experiences for critically ill patients in Canada.
Using Image Processing to Identify Presumptuous Macrophages in Retinal Scans

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BACKGROUND: Tumour Associated Macrophages (TAMs) play a role in cancer biology and are present in malignant melanoma but absent in benign nevi (freckles). In a pilot clinical study, we observed small hyperfluorescent dots (SHDs), presumptive TAMs (pTAMs), in the eyes of patients with ocular melanoma but not nevi.

RATIONALE: In this study, we hypothesize that computer algorithms can be generated and trained to identify similar SHDs within retina scans by (1) describing and replicating the properties of the SHDs, (2) simulating these SHDs and placing them within real images, and (3) training and testing these algorithms for their precision and recall compared against human manual counting.

METHODS: With informed patient consent, we used preexisting data to assess the size distribution, intensity distribution, and position of SHDs within each image. These points were then simulated in a realistic manner utilizing Airy Disks and several test distribution functions (Laplacian of Gaussian, Difference of Gaussian, and Determinant of Hessian)[1]. Simulated SHDs were then placed onto a healthy retinal scans, and multiple algorithms developed and evaluated for their precision and recall[2][3]. These algorithms were compared against human performance using the same images.

RESULTS: Human graders detected SHDs with a specificity of $2.208 \times 10^{-5}$ and a sensitivity of 0.245. The computer algorithm detects with a specificity of $9.023 \times 10^{-6}$ and a recall rate of 0.239 while taking at least 10 times less time than that of a human detector.

CONCLUSION: We have written a program that is capable of detecting SHDs in the eyes of patients and is comparable in its performance to that of a human grader, while requiring less time. The ability to identify pTAMs in the eyes of patients with a spectrum of tumours has the potential to be a useful diagnostic tool, and early analysis of human images suggests it is clinically utility.

Describing Fertility in Men with Cystic Fibrosis
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BACKGROUND: Infertility in males with Cystic Fibrosis is well documented, with around 98% of men demonstrating azoospermia secondary to congenital bilateral agenesis of the vas deferens (CBAVD)(Kaplan et al., 1968). As spermatogenesis is still normal in these individuals, there is the potential of having children through assisted reproductive technology, usually sperm aspiration combined with ICSI. To date, there have been no large scale studies assessing the reproductive outcomes in men with CF. This study aims to address this issue.

OBJECTIVE: To better understand the knowledge, attitudes and practices of men with CF regarding their reproductive potential and options for fertility treatment.

METHODS: A survey will be conducted of males age 20-75 years of age currently in attendance at the CF clinic at St. Michaels Hospital. Questions will centre around their attitudes towards starting a family and their experience with trying to do so. The survey will be distributed by email to patients at routine clinic visits. It is expected that it will take between 6 months – 1 year to collect the required data.

Sponsorship: The Keenan Research Summer Student Program

Exploring the barriers to use of end-tidal CO2 monitoring during In-Hospital Cardiac Arrest

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Background: Monitoring end-tidal carbon dioxide (ETCO2) provides real-time data on the quality of resuscitative attempts, which is crucial for survival from in-hospital cardiac arrest (IHCA).1 The aim of the study was to identify barriers that responders encounter in implementing ETCO2 monitoring during IHCA events at St. Michael’s Hospital.

Methods: Using purposive sampling, a total of 56 healthcare professionals including residents, anaesthesiologists, nurses and respiratory therapists were recruited to participate in a qualitative study. Six focus groups were conducted over a 9-month period (2017-2018). Interviews were tape-recorded and transcribed verbatim. Transcripts were imported into NVivo software, and then analysed using qualitative thematic analysis.

Results: The data suggested three principal themes of barriers to monitoring ETCO2. (1) Practical challenges: challenges existed with setting up ETCO2-equipped defibrillators. Further limitations included a lack of space and time during resuscitation, along with a shortage of team members familiar with ETCO2 equipment. (2) Questions about ETCO2 data usage: participants questioned whether ETCO2 data was incorporated into decision making during an IHCA. Lack of communication and understanding about the ETCO2 data was prevalent amongst team members and affected their motivation in recording and using the information. (3) Problems with simulation training program: participants criticized the simulation environments as being unrealistic with respect to difficulties encountered with setting up ETCO2 monitors. Simulation rooms were spacious and organized with equipped defibrillators properly set up, whereas a real-time IHCA situation was small and chaotic. Additionally, training was only delivered during daytime for staff, such that not all responders were able to undergo training prior to attending an IHCA.

Conclusion: The study suggests that realistic modification of simulation trainings could address some of these barriers. Furthermore, training teams on ETCO2 interpretation and how to best use the data could lead to beneficial usage of ETCO2 during IHCA.

Motion Analysis in Endoscopic Surgery: Development of an Enhanced Simulation Platform to Aid in Resident Training

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INTRODUCTION: Motion analysis in surgical simulation has been well studied within laparoscopic surgery. Motion-tracking can provide valuable data to improve psychomotor skills, and can serve as a more formative evaluative tool. Motion analysis, however, has not been well studied in endoscopic surgery, with almost no studies examining flexible ureteroscopy (fURS). This procedure is currently the most common surgical practice for treating kidney stones and can have a steep learning curve.

METHODS: We aimed to develop a ureteroscopic surgery simulation platform that incorporates instrument motion-tracking capabilities. An existing benchtop ureteroscopy model (Cook Medical™) was fitted with motion-tracking software (Polhemus™) and feasibility testing was performed. The task was to visualize all upper, inter, and lower pole calyces. Instrument motion-tracking and video recording of hand motions were captured. Metrics were established and key degrees of freedom (DOF) for fURS were identified. A survey study was completed to identify the challenges trainees face with fURS.

RESULTS: We developed a functional ureteroscopy simulation platform that incorporates tool motion-tracking. We analyzed motion DOF which best capture instrument motion in fURS: 1. in-out motion, 2. scope rotation, and 3. scope tip flexion. Preliminary testing revealed that these metrics can potentially easily distinguish ureteroscopy performed by a novice vs. an expert surgeon. A survey study identified potential areas of focus for future fURS simulation training, such as accessing lower pole calyces of the left kidney with comfortable rotation of the hand, particularly for difficult anatomies.
INTRODUCTION: Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare inflammatory disease of the central nervous system, which primarily affects the optic nerves and spinal cord. Research has demonstrated that candidate risk factors for the development of NMOSD include smoking, sun exposure, vitamin D status, obesity, diet, early childhood infection, and delivery type at birth. However, these research studies tended to be retrospective and uncontrolled case studies. Therefore, there is a lack of studies investigating the environmental and personal exposures in NMOSD.

OBJECTIVE: The objective of the study is to use a case control study design to investigate the association between various environmental and personal risk factors and NMOSD. These will include gender, ethnicity, diet, hormonal exposures, smoking, comorbidities, physical activity, and infectious exposures.

METHODS: Participants were recruited from St. Michael’s Hospital and were identified using the 2015 International Panel for NMOSD diagnosis (IPND) criteria. Aquaporin-4 antibody positive and negative cases as well as myelin oligodendrocyte glycoprotein positive cases were included. The validated EnvIMS questionnaire was used to collect demographic data from participants.

RESULTS: Preliminary descriptive data from our NMOSD cohort will be presented.

CONCLUSION: Knowledge of the association between NMOSD and various exposures can facilitate efforts to prevent this highly disabling neurologic disease.

References:
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**Chronic child maltreatment as a neurodevelopmental disorder: insights from machine learning**

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**OBJECTIVE:** To use machine learning to investigate patterns in neuropsychological and qualitative data among survivors of chronic childhood maltreatment compared to unaffected healthy controls.

**DESIGN:** Participants were recruited as a part of a large, observational study (Strategic Applied Injury Research [STAIR]) of head trauma in five predetermined groups: non-traumatic brain injury (TBI) control group, crown wards, homeless, TBI, and partner batterers. All participants that were included underwent a series of assessments, including self-report scales and clinical questionnaires, neuropsychological testing batteries, and semi-structured interviews. Using the interview as a determining factor, participants were assigned a value related to the severity of their abuse. We defined ‘chronic child maltreatment’ (CCM) as the persistent pattern of emotional, physical, and/or sexual abuse or neglect from at least one primary caregiver during childhood or early adolescence (<16 years of age). Participants assigned a 2 clearly met this definition while those assigned a 0 did not; if it was unclear if the participant sustained persistent abuse they were assigned a 1. Machine learning will be implemented by initially preprocessing the domains (self-report scales and clinical questionnaires, neuropsychological testing batteries, and semi-structured interviews) into various variables, and clustering those variables based on similarities which are determined from specific algorithms used. These clusters will be analyzed to determine how closely they are correlated to the CCM codes.

**FINDINGS:** My results will show patterns and relationships of the variables that were previously extracted from the domains.

**CONCLUSION:** Insights from this study will identify the most effective avenues for minimizing harms.

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Physiological Effects of Supine versus Upright Exercise in Patients with Hepatopulmonary Syndrome (HPS) and Orthodeoxia

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Hepatopulmonary syndrome (HPS) is a rare abnormality of the pulmonary vasculature, found in a subset of patients with liver cirrhosis. About 25% of patients with HPS, have concurrent platypnea and orthodeoxia, characterized by an improvement in their shortness of breath and oxygenation when supine compared to upright. While liver transplantation is considered to be the only effective therapy for HPS, exercise has been shown to slow deterioration of their condition and improve transplant outcomes. Although HPS patients with orthodeoxia are limited in their ability to exercise by their dyspnea, cirrhosis, and hypoxemia, their arterial oxygenation and dyspnea are improved in the supine position. In this report, we present the study protocol for a randomized controlled cross-over clinical trial testing the effect of supine position on exercise parameters and compare them to traditional upright exercise, in patients with HPS and orthodeoxia. We will randomly assign 10 participants with HPS and clinical orthodeoxia to begin with a supine or upright exercise regimen on a cycle ergometer. Subsequently, all participants will complete the alternate test within 4 weeks. The primary outcome will be the participant’s tolerance limit (tLIM), defined as the time elapsed until exhaustion or pre-defined safety criteria are reached. We hypothesize that tLIM will be significantly higher when performing supine exercise, as opposed to upright. This approach of a supine exercise intervention could enable these patients to garner the cardiovascular and respiratory benefits of exercise. In particular, improved cardiovascular capacity may be of critical importance in advance of liver transplant surgery, and may improve transplant outcomes. **Funding sources:** This study will be funded by the Michael Locke Term Chair in Knowledge Translation and Rare Lung Disease Research.
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