



Western University  
Schulich School of Medicine & Dentistry  
**Department of Medicine**

**RESEARCH DAY**

Friday, May 11, 2018  
Best Western Lamplighter Inn  
591 Wellington Road South  
London, Ontario N6C 4R3

This program has no commercial support.

## CME INFORMATION

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by Continuing Professional Development, Schulich School of Medicine & Dentistry, Western University. You may claim a maximum of 4.0 hours (credits are automatically calculated).

Each participant should claim only those hours of credit that he/she actually spent participating in the educational program.

### Learning Objectives:

- To describe new research findings of relevance to Internal Medicine and related subspecialties.
- To appreciate clinical research conducted by the trainees in the Department of Medicine.
- To appreciate basic research conducted by trainees in the Department of Medicine.



Scan the QR code to complete the Participant Evaluation form online.

**Department of Medicine  
Resident Research Day 2018**  
Friday May 11, 2018  
Best Western Lamplighter Inn  
591 Wellington Road South

Start		End		Schedule of Events	
8:00	8:30	<b>Breakfast</b>		<b>Poster Setup</b> (Crystal Ballroom South)	
8:30	8:40	<b>Welcome &amp; Opening Remarks</b> (Crystal Ballroom North)			
8:40	9:40	<b>Trainee Oral Presentations – (4)</b> (Crystal Ballroom North) <i>10 min presentation 5 min Q&amp;A</i>			
9:40	10:00	Paying <b>Attention</b> to Delirium <b>Dr. Niamh O’Regan</b> (Crystal Ballroom North) <i>15 min presentation 5 min Q&amp;A</i>			
10:00	11:00	<b>BREAK</b>		<b>Poster Presentation and Judging</b> (Crystal Ballroom South)	
11:00	11:45	Whose work is it? Teamwork, Collective Competence and the Myth of Individual Performance Assessment <b>Keynote - Dr. Lorelei Lingard</b> (Crystal Ballroom North) <i>40 min presentation 5 min Q&amp;A</i>			
11:45	13:45	<b>LUNCH</b>		<b>Poster Presentation and Judging</b> (Crystal Ballroom South)	
<b>Afternoon Session – Highlight Research by Department of Medicine Trainees</b>					
14:00	15:15	<b>Trainee Oral Presentations – (5)</b> (Crystal Ballroom North) <i>10 min presentation 5 min Q&amp;A</i>			
15:15	15:30	<b>Presentation of Awards &amp; Final Remarks</b> (Crystal Ballroom North)			
15:30	15:45	<i>Please ensure that you complete the program evaluation form before you leave for the day. The online version is <a href="https://www.surveymonkey.com/r/ParticipantsEval2018">https://www.surveymonkey.com/r/ParticipantsEval2018</a> or hard copies can be found at the Registration Desk.</i>			

## Oral Presentations

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## **An Evaluation of Utilization Patterns and Appropriateness of Laboratory Tests among New Referrals to Rheumatologists: Choosing Unwisely!**

**Azin Ahrari**, Sierra Skye Barrett, Gina Rohekar, Sherry Rohekar, Pari Basharat, Sarah Haig, Janet Pope.

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**Background:** Autoantibodies are common investigations ordered by physicians in diagnosing rheumatic diseases. Rheumatoid factor (RF) and antinuclear antibody (ANA) have been shown to have low positive predictive value in patients in general practice. The Canadian Rheumatology Association (CRA) Choosing Wisely Canada Campaign developed a list of 5 tests with evidence indicating they may not be adding value. **Objective:** To evaluate the utilization patterns, appropriateness, and associated cost of autoantibody testing (ANA, ENA, anti-dsDNA, RF) in patients referred to rheumatology. **Methods:** A chart audit reviewing the records of 500 referred patients was conducted. Specific tests and their indication based on clinical presentation were extracted. The number of unnecessary laboratory tests and associated cost was calculated. **Results:** Most common referrals were for possible diagnosis of rheumatoid arthritis, lupus, and seronegative spondyloarthropathies. Prior to referral: 77% had ANA testing at least once, in one-third of cases, ANA was repeated; 25% had ENA testing and 30% had anti-dsDNA. Among all ANA tests, 25% were requested with no clinical indication based on American College of Rheumatology criteria. 50% of ENA and anti-dsDNA was requested in the context of negative ANA. RF was requested in 65% of the referrals and one third had no clinical indication. **Discussion:** RF, ANA, ENA, and anti-dsDNA are among commonly ordered investigations. Despite the recommendations by CRA choosing wisely campaign up to 50% of tests are inappropriately ordered. Based on cost estimation, more selective ordering of the above tests would lead to 45% cost reduction.

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## **Patterns of Reasoning Tasks Used During Clinical Case Review in Ambulatory Setting: Implications for Competency Based Training**

**Azin Ahrari**, Kamilah Abdur-Rashid, Jacqueline Torti, Mark Goldszmidt.

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**Background:** Reasoning tasks have been proposed as a method for describing and analyzing clinical practice during a patient encounter that take into account more holistic conceptualization of expert practice. In prior studies, we identified a unified list of 24 reasoning tasks that physicians engage in during clinical encounters. **Purpose:** 1. Identify the reasoning tasks addressed in ambulatory setting 2. Identify number of tasks addressed during each encounter. 3. Identify the tasks that residents required support from the attending. **Methods:** The data collection and analysis was guided by the constructivist grounded theory methodology. A constant comparative approach was utilized to analyze the transcripts of 40 case reviews. **Results:** On average 10 reasoning tasks were addressed during each encounter. There were four dominant tasks. Identifying active issues and establishing management plans were two overarching tasks. Of the supportive tasks assessing severity and rate of progression, response to treatment and estimating prognosis were the most addressed reasoning tasks. Attending helped residents elaborate on some tasks : 1. identifying complications associated with the diagnosis, diagnostic investigations, or treatment; 2. determining follow up, monitoring strategies; 3. Assessing rate of progression, response to treatment and estimating prognosis 4. Weighing alternative treatment options. **Conclusion:** This study provides further insight into reasoning tasks utilized by physicians in ambulatory setting. We identified tasks that are commonly addressed and those that were missed or required further elaboration by the supervisor. These findings support CBME by helping judge trainee stage of competence and articulate potential areas of improvement.

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## **Treatment of Venous Thromboembolism in Acute Leukemia: a Systematic Review**

**Azin Ahrari**, Fatimah Al-Ani, Yimin Pearl Wang, Alla Iansavitchene, Alejandro Lazo-Langner.

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**Background:** Patients with hematologic malignancies are up to 26 times more likely to develop venous thromboembolism (VTE) than the general population. The standard treatment for VTE is anticoagulation, however, its safety and efficacy in this patient population has not been formally evaluated. In addition, severe thrombocytopenia and coagulopathies in patients with hematologic malignancies makes treatment of VTE challenging. **Methods:** We conducted a systematic review of the literature describing treatment of VTE in the setting of acute leukaemia (AL). Due to the heterogeneity of findings, no meta-analysis was attempted. **Results:** A total of 13 observational studies, including 11 cohort studies and 2 case control studies, were included with 5,359 participants. Number of patients who developed VTE among the total population was 330 (6.2%; 95% CI 5.5-6.8). Of patients with VTE, 229 patients received treatment with anticoagulation. Agents used for anticoagulation included low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), and vitamin K antagonists (VKA). Most studies adjusted dose of anticoagulant based on platelet (PLT) counts. Most commonly, LMWH dose was reduced by 50-75% for PLT counts less than  $50 \times 10^9 /L$ . Many studies temporarily held anticoagulation in the face of severe thrombocytopenia ( $PLT < 10 \times 10^9 /L$ ) refractory to transfusions. **Conclusion:** Our systematic review obtained information about anticoagulation regimens for treatment of VTE in AL patients. There is a high degree of heterogeneity in choice of anticoagulant and dose adjustments. Further studies are required to develop guidelines and suggestions for treatment of VTE in AL.

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## **5-ASA use in Crohn's Disease and Ulcerative Colitis: a city-wide cross-sectional analysis**

**Hisham Akhtar**, Dr. Maan Alkhattabi, Dr. Jamie Gregor, Dr. Nilesh Chande, Dr. Vipul Jairath.

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**Background:** 5-ASA use in Crohn's Disease (CD) remains a controversial topic with variability in evidence regarding their efficacy in inducing remission. With this in mind, there remains variability in use of 5-ASA in patients with CD. Relapse rates in patients with CD following 5-ASA withdrawal have yet to be studied. This study is a city-wide cross-sectional analysis to determine 5-ASA use in CD and Ulcerative Colitis (UC) in London, Ontario, Canada. This is a preliminary study to the upcoming STATIC trial that will determine whether ongoing use of 5-ASA in CD's is efficacious. The aim was to determine the city-wide prevalence of 5-ASA use in patients with CD and compare it to its use in UC. The use of biologic therapy, immunotherapy and steroid use was also analyzed. **Methods:** Patients seen in tertiary care IBD clinics in London, Ontario (Victoria Hospital, University Hospital and St. Joseph's Hospital) between January and June 2016 were reviewed. All patients diagnosed with UC and CD were included in the study. Patients with indeterminate colitis were excluded. For patients seen on multiple occasions over the review period, their medication profile was derived from their last visit. Chi squared analysis was used for comparison of proportions. **Results:** 1200+ patients were included in the study, including X UC patients (X%) and Y CD patients (Y%). In total, \_\_\_% of patients were using 5-ASA ( \_\_\_% UC; \_\_\_% CD). Full results and conclusions to be added at a later date.

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## **Generation and Characterization of a Novel Mouse Model for Studying Atherosclerosis in Patients with Rheumatoid Arthritis**

**James Akingbasote**, Ewa Cairns, Murray Huff, Geoffrey Pickering, Lillian Barra.

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Cardiovascular disease (CVD) is a major cause of death in patients with rheumatoid arthritis (RA). To generate a novel mouse model to study the co-morbidity of RA and atherosclerosis, mice transgenic for human DR4, the strongest genetic risk factor for RA, were cross-bred with LDL receptor knock-out (Ldlr<sup>-/-</sup>) mice. Ldlr<sup>-/-</sup> mice are known to develop atherosclerosis when fed a high-fat diet. Following 5 generations, mice were genotyped by PCR to assess the expression of the DR4 and Ldlr. Further, 6-8 week-old DR4Tg, Ldlr<sup>-/-</sup> and DR4TgLdlr<sup>-/-</sup> mice were fed a high-fat, high-cholesterol (HFHC) diet or a control chow diet for 12 weeks. Blood was obtained and analysed for glucose levels and serum assayed for lipoproteins. Heart, aorta, liver and the limbs were collected, and sections stained by haematoxylin and eosin (H&E). The aortic sinus was stained by H&E to determine plaque size. En face preparation of the aorta was stained with SUDAN IV to assess plaque surface area. Knee joint sections were stained for the presence of arthritis. PCR showed that the DR4TgLdlr<sup>-/-</sup> mice expressed human DR4 mRNA but not Ldlr<sup>-/-</sup> mRNA. In HFHC-fed, but not chow-fed DR4TgLdlr<sup>-/-</sup>, plasma total and LDL cholesterol were significantly increased and plaque surface area in the aorta was readily apparent. With the stable expression of the human DR4 and not the Ldlr, DR4TgLdlr<sup>-/-</sup> mice have the potential for use as a model for studying atherosclerosis in RA.

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### **A Systematic Review of Predictors of Venous Thromboembolism in Acute Leukemia**

**Fatimah Al-Ani**, Azin Ahrari, Pearl Wang, Alejandro Lazo-Langner.

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**Background:** Risk factors for development of venous thromboembolism (VTE) in acute leukemia (AL) are unknown. **Methods:** We conducted a systematic review of RCTs and observational studies assessing VTE in AL including acute myeloid leukemia (AML), acute promyelocytic leukemia (APL) or acute lymphoid leukemia (ALL). Relative Risks (RR) for all VTE events, catheter related thrombosis (CRT) and cerebral vein thrombosis (CVT) were calculated. **Results:** A total of 30 studies were assessed with 15, 491 AL participants. Of the

total participants, the number of evaluable patients was 10,788 for AML, 3,242 for ALL, and 1,031 for APL. The median time of VTE occurrence from diagnosis was ranging between 5 and 92 days. The risk of VTE was around 2-fold significantly higher in ALL compared to AML (excluding APL) [RR: 1.8; 95%CI: 1.58-2.10; p<0.00001]. When comparing APL to other AML subtypes, thrombosis risk was 1.5-fold significantly higher in APL [RR: 1.56; 95%CI: 1.24-1.97; p=0.0001]. The thrombosis risk was significantly higher with the presence of catheter [CRT vs. non-CRT: RR: 1.2; 95%CI: 1.04-1.36; p=0.0074]. The risk was also similar between PICC line vs. central catheter [RR: 1.08; 95%CI: 0.81-1.45; p=0.557]. For CVT, the risk was 4-fold higher with ALL patients compared to AML patients [RR: 4.1; 95%CI: 1.75-9.73; p=0.0012]. **Conclusion:** Factors that seem to influence this VTE risk are AL subgroup, and the presence of catheter. The risk of thrombosis seems to be higher in the initial period following diagnosis.

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### **External validation of the Park score for bowel preparation cleanliness during capsule endoscopy**

**Mohammad Alageeli**, Yan, Brian; Zepeda-Gomez, Sergio; Alshankiti, Suliman; Bahreini, Zoya; Homenauth, Ravi; Thomas, Benson; Stitt, Larry; Rofaiel, Rymon; Yoo, David; Al-Zahrani, May; Townsend, Cassandra m.; Jarosh, Jennifer; Smith, Alexis; Singh, Chantal; Kloc, Milica; Gilani, Syed O; Friedland, Joshua; Luhoway, Jacqueline; Merotto, Lucas; Dang, Thuchhi; Sey, Michael.

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**Background:** Capsule endoscopy is the test of choice for small intestinal diseases although it can be limited by poor bowel preparation. The Park score measures small intestinal cleanliness based on the % of mucosa visualized and % of view obstructed and is a promising tool for assessing small bowel preparation. **Methods:** A total of 20 readers: 4 capsule endoscopists, 4 GI fellows, 4 internal medicine residents, 4 medical students, and 4 nurses were invited to participate in the study. All readers completed a web-based Training Module on the Park score followed by an Assessment Module which was repeated 4

weeks later. The Assessment Module consisted of 1,233 images derived from 25 randomly selected capsule videos. Images were selected at 5 minute intervals of each video and readers rated the % of the mucosa visualized and the % of view obstructed as defined by the Park score. The primary outcome was inter-observer and intra-observer agreement for the total score. Results: The mean inter-observer and intra-observer agreement for the total Park score between all readers was 0.81 (95% CI 0.70-0.87) and 0.92 (0.87-0.94). Stratified by sub-scores, the mean inter and intra-observer agreement for % visualized mucosa was 0.79 (0.67-0.85) and 0.91 (0.86-0.93) and for % of view obstructed was 0.77 (0.64-0.84) and 0.91 (0.87-0.94). Conclusion: The Park score is a simple and reliable scoring system to measure small intestinal cleanliness with excellent agreement between a wide range of readers with varying levels of experience with capsule endoscopy.

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### **Comparison of cerebral blood flow response to CO<sub>2</sub> between chronic kidney disease patients (CKD), hemodialysis patients (HD), and healthy individuals.**

**Rehab Albakr**, Rehab Albakr<sup>1</sup>, Tanya Tamasi<sup>1</sup>, Justin Dorie<sup>1</sup>, James Duffin<sup>2</sup>, Christopher McIntyre<sup>1,3</sup>, Marat Slessarev<sup>1,3</sup> Departments of Medicine<sup>1</sup> and Medical Biophysics<sup>3</sup>, University of Western Ontario Department of Physiology<sup>2</sup>, University of Toronto.

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**BACKGROUND:** CKD and HD patients experience higher rates of cerebrovascular disease and cognitive decline compared to the general population. These changes may be related to impairment in cerebrovascular circulation, and specifically in its ability to respond to hemodynamic stress. Cerebral blood flow (CBF) response to carbon dioxide (CO<sub>2</sub>) can be used to assess cerebrovascular function non-invasively, allow early detection, evaluation, and monitoring of vascular disease progression, and provide means for evaluating effectiveness of preventative, therapeutic and rehabilitative interventions in these patients. **OBJECTIVE:** To test the feasibility of measuring CBF response to CO<sub>2</sub> in CKD and HD patients, and to compare its magnitude and dynamics to that of healthy

volunteers. **HYPOTHESIS:** CBF response to CO<sub>2</sub> will be different between healthy individuals, CKD and HD patients, with healthy volunteers showing the best and HD patients the worst response. **METHODS:** We used RespirAct™ to induce a 10-mmHg square wave change in end-tidal PCO<sub>2</sub> (PETCO<sub>2</sub>) from normocapnia to hypercapnia and back to normocapnia in ten healthy volunteers, ten CKD and ten HD patients while monitoring CBF using transcranial Doppler and global hemodynamics using Finapres NOVA. The magnitude and dynamics of CBF response to CO<sub>2</sub> will be measured as % changes in CBF per mmHg change in PETCO<sub>2</sub> and as half-life of change respectively for both increase (normocapnia → hypercapnia) and decrease (hypercapnia → normocapnia) in CO<sub>2</sub>. Comparisons between groups will be done using ANOVA with statistical significance assumed if p < 0.05. **RESULTS:** will be presented in research day

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### **A Large Familial Pathogenic PKP2 deletion Manifesting as Lone Atrial Fibrillation: Further Evidence for Atrial Cardiomyopathy as a Sub-Phenotype of the Arrhythmia**

**Saad Alhassani**, Jason Roberts.

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**Introduction:** Atrial fibrillation (AF) is the most common arrhythmia of clinical significance. Recently there was a preponderance of evidence suggests a large genetic contribution to atrial fibrillation (AF). Plakophilin-2 gene mutation is one of the desmosomal genes mutation causing myocyte loss and fibrous and fatty tissue replacement which result in right ventricle dilatation and life-threatening arrhythmias and sudden cardiac death ARVC. **Case presentation:** We describe two brothers with PKP2 deletion which seems to be pathogenic in the absence of any structural or electrical features of ARVC based on Task force criteria and they were found to have a Lone Atrial Fibrillation, they have PKP2 pathogenic deletion and family history of sudden cardiac death. Both of them were seen in the clinic for ARVC workup. **Case 1:** 30 years old male. He has two syncopal episodes which seems to be related to alcohol, loop recorder showed

persistent AF, no history of palpitation, he was found to have atrial fibrillation on ECG, Echo showed moderate bi atrial enlargement, MRI was not suggestive of ARVC based on task force criteria. Case 2: 27 years old male competitive athlete. He has no palpitation, syncope, chest pain. ECG showed AF. MR heart showed bi ventricular dilatation suggestive of athlete heart with no ARVC features. Echo showed borderline dilated right ventricle. Conclusion: These findings support the hypothesis that AF in certain patients is reflective of atrial cardiomyopathy and desmosomal mutation in ARVC can contribute to isolated atrial cardiomyopathy.

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### **Simplified HOSPITAL Score Validity to Predict Unplanned All-Cause 30-Day Hospital Readmissions**

**Mohanad Almaimani, Saira Zafar.**

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**Objective:** We aimed to check the validity of the original and simplified versions of the HOSPITAL score on our patient population. **Methodology:** We retrospectively screened 200 patients discharged from medical department at Victoria Hospital in London, ON between January 1st 2017 and June 30th 2017. The main outcome was any unplanned 30-day hospital readmission. We simplified the score as follows: (1) "discharge from oncology division" was replaced by "cancer diagnosis or discharge from oncology division". (2) procedures were omitted. (3) patients were categorized into two risk groups (likely and unlikely) instead of three groups. The risk categorization was done on three different cut off points. **Results:** Out of 200 patients discharged from medical department 173 (86.5%) patients were included in data analysis. Overall, the median for both original and simplified HOSPITAL scores was 4 points. HOSPITAL score can be best applied to our patient population when the cut off point is at 3, where both the original and simplified scores classified 23.7% (n= 41) discharges as unlikely to be readmitted. On the other hand, 76.3% (n=132) discharges were classified as likely to be readmitted based on the original score and 74.6% (n=129) discharges were classified as likely according to the simplified one. This means only 1.7% (n=3) discharges were classified differently

between the two score versions. **Conclusion:** Simplified and original scores have shown similar results regardless of the cut off point value. Our study suggests that simplified HOSPITAL score is better to be used for prediction of 30-day readmission risk.

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### **Improving the Follow Up of Patients at the Endocrinology Clinic after Hospital Discharge**

**Haifa Alnahdi, MD, FRCPC; Ranjit Syngarayer, MD, FRCPC; Amanda Berberich, MD, FRCPC; Kristin Clemens, MD, FRCPC.**

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**Objective:** To provide timely outpatient follow up for patients seen by the urgent endocrine consult team while admitted to hospital. **Background:** Upon their discharge, patients with urgent endocrine conditions should be prioritized and seen within an appropriate timeframe. Delayed follow-up times might be associated with increased morbidity, higher readmission rates and unsatisfactory patient care. It is often challenging for physicians to accommodate these appointments in their busy clinic schedules. **Method:** We identified all patients referred to our inpatient consultation service during an admission to University or Victoria Hospital between (Sep 2017 and Jan 2018). We then identified those patients who required timely follow up (ie. 6 weeks) by one of our consultant physicians. The need for urgent follow up was made based on the team judgement. Before their discharge, an outpatient appointment was made with their endocrinologist. We then tracked the time between their discharge to their follow up appointment. We also did a survey of our medical secretaries to understand their visit organizing processes, and the stress level they face booking these appointments. **Results:** 18 patients (95%) were scheduled an appointment within 6 weeks of hospital discharge, with 17 patients (90%) actually seen and one no show. The remaining patient attended an appointment at 8 weeks. **Conclusion:** Patients seen by our service were seen within a timely fashion after hospital discharge. However, we identified some difficulties organizing these appointments. Efforts to streamline our discharge processes will be explored.

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## **Fever, cholestatic hepatitis and pneumonia, a common presentation of an uncommon disease: case report and literature Review**

**May Alzahrani**, Joana Walsh, Karim Qumosani, Anouar Teriaky.

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**Background:** Q fever is a zoonotic infection caused by *Coxiella burnetii* and usually acquired by susceptible patients in a presence of described risk factors. Known manifestations of it include fever of unknown origin, endocarditis, atypical pneumonia, and hepatitis. **Aims:** To describe an interesting case of Q fever and review the literature on Q fever and hepatic manifestations. **Methods:** Patient information was extracted from electronic records and included admission notes, laboratory investigations, procedure reports, pathology notes and clinic reports. In addition, we conducted a literature review on Q fever hepatitis through the pubmed database to review epidemiology, different presentations, diagnosis, and treatment. **Results:** We are reporting a case of a 48 years old male with no recognizable risk factor who presented with fever, pneumonia, cholestatic hepatitis, anasarca and coagulopathy. He had an extensive negative workup and definitive diagnosis was only made after the results of a liver biopsy showed Q fever's typical finding of a fibrin ring granuloma. He was started on treatment with an 18 month course of doxycycline resulting in full recovery. North American data showed increasing number of Q fever cases being reported to CDC. In Canada, the national incidence is not known. Hepatic manifestations of Q fever include mild to moderate transaminitis, cholestasis, hepatic abscesses, triggering of autoimmune hepatitis/PBC overlap and acute calculus cholecystitis. **Conclusions:** The incidence of Q fever is increasing with a wide spectrum of presenting symptoms. In the presence of atypical hepatitis, investigations should be conducted to rule out Q fever.

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## **Interventions to optimize adenoma detection rate– a systematic review and meta-analysis of the literature**

**Anshul Arora**, Cassandra McDonald, Allansavitchene, Dr. Mayur Brahmania, Dr. Michael Sey.

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**Introduction:** Colorectal cancer is the second leading cause of cancer related deaths in Canada. The adenoma detection rate (ADR), i.e., the proportion of average risk patients with at least one adenoma detected during screening colonoscopy, is inversely associated with the development of interval colorectal cancer. Factors that increase ADR have become an important focus of quality improvement. The objective of this study is to conduct a systematic review and meta-analysis of the literature to evaluate the efficacy of endoscopist targeted interventions to improve adenoma detection rate, which include withdrawal time, withdrawal technique, in room observers, physician report cards, and quality improvement and training programs/measures. **Methods:** Systematic searches were conducted to identify potentially relevant studies in MEDLINE, Embase, Cochrane Central Register of Controlled Trials databases, and the NIH ClinicalTrials.gov with the aid of a research librarian. Both randomized controlled trials (RCT) and observational studies were included. Included studies assessed an intervention aimed at optimizing endoscopist performance on ADR during colonoscopies. Studies that evaluated interventions aimed at improving procedural or technological factors, or that consisted exclusively of specific patient sub-groups with high risk for colorectal cancer were excluded. Risk of bias was assessed using the Newcastle Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for RCTs. **Results:** 4299 titles and abstracts will be screened by two reviewers for inclusion in the study. Further literature search and full text analysis ongoing and expected to be complete prior to presentation date.

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### **Systematic review of scoring systems for recurrence of hepatocellular carcinoma after liver transplantation**

**Salman Aziz**, Karim Qumosani.

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**Introduction:** Recurrence of hepatocellular carcinoma (HCC) after liver transplantation is a major cause of morbidity and mortality. Several risk assessment tools have been developed, although to date, there is no widely accepted tool to predict HCC recurrence. The aim of the current study was to critically appraise published literature on HCC recurrence scoring systems. **Methods:** An electronic data base search was performed using MEDLINE, EMBASE, Cochrane library, and Central Registry of Clinical Trials. All retrospective chart reviews and validation studies that analyzed scoring systems with clinical and explant pathologic characteristics to determine recurrence of hepatocellular carcinoma post-transplant between 2000-2017 were included. **Results:** The literature search identified 146 studies, of which 140 were excluded. From the six scoring systems three studies have been validated. **Conclusion:** Several scoring systems exist to classify risk of HCC recurrence post-transplant. A validated scoring system may help clinicians identify high risk patients which may require stringent surveillance strategies.

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### **Development of a Novel In Vitro System to Assess the Feasibility of Utilizing Exogenous Surfactant as a Pulmonary Drug Delivery Vehicle**

**Brandon Baer**, Cory Yamashita & Ruud Veldhuizen.

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**Background:** Due to its complex branching structure, direct drug delivery to small and distal airways of the lung is a major challenge. Consequently, most therapies targeting pulmonary infections and inflammation, utilize high dose systemic administration, with the potential for adverse side effects. Our lab has been investigating the use of exogenous surfactant, to facilitate the delivery of

intrapulmonary therapeutics in a more direct and efficient manner. **Objectives:** Develop and utilize an in vitro transferring system to assess exogenous surfactant as a pulmonary drug delivery vehicle. **Methods:** The Wet Bridge Transfer system was developed to simultaneously study surfactant delivery and drug efficacy. It consisted of two connected wells in which drugs were instilled into an administration well and function was tested in a remote well. The distal wells were seeded with either bacteria or stimulated macrophages. Then therapeutics were administered to the delivery well alone or in combination with surfactant. **Outcomes** involved spot plating for bacterial killing and cytokine analysis for anti-inflammatory effects. **Results/Discussion:** Administering any of the antimicrobial or anti-inflammatory drugs to the delivery well without surfactant resulted in no change for outcomes in the remote well, indicating poor drug delivery. However, bacterial growth in the remote well was reduced by several surfactant/antibiotic preparations, and a few surfactant/anti-inflammatory mixtures lowered its pro-inflammatory cytokine concentrations. This system can be used to rapidly assess and screen surfactant-based therapies prior to their assessment in vivo. Furthermore, our results indicate that exogenous surfactant was an effective delivery vehicle for many antimicrobial and anti-inflammatory therapeutics.

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### **Therapeutic drug monitoring (TDM) in patients with ulcerative colitis treated with golimumab**

**Zoya Bahreini**, Jamie Gregor, Pauline Walton-Mennill.

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**Background:** Anti-tumor necrosis factor is a mainstay of treatment in patients with inflammatory bowel disease refractory to traditional therapies. The most recent anti-TNF that obtained its marketing license for treatment of ulcerative colitis is Golimumab (GLM). The PURSUIT trial strongly suggested that high GLM trough levels correlated with patients' improvement. Although, there is no consensus on what constitutes an adequate trough level, a trough level of 2.5 µg/ml has been suggested to optimize clinical response. **Aims:** To determine

the proportion of patients with UC on GLM who obtained adequate trough levels of GLM. Methods: This is a retrospective cross-sectional analysis of GLM levels and antibodies to GLM (ATG) inpatients with UC treated between December 2015 and October 2017. Results: 40 patients were initiated on GLM in the study period. TDM was available on 11 patients. The mean GLM trough level was 2.58 with a median of 1.43. Only 3/11 of patients had a trough level above the level suggested for optimal clinical response. All patients had measurable drug levels. 3 patients with trough levels below had their dose doubled, resulting in a mean increase of 1.27 but only 1/3 obtained a level above 2.5. None of the patients had measurable levels of ATG. Conclusions: Although ATG appear to be rare with GLM administration, the traditional dosing regiment appears to produce trough levels that may not be adequate for an optimal clinical response. Use of an initial maintenance dose higher than 100mg every 4 weeks may prove to be more effective.

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### **Closure of Patent Foramen Ovale or Medical Therapy After Cryptogenic Stroke: Systematic Review and Meta-Analysis**

**Shahrukh N. Bakar, BSc (Hon.) MD FRCPC,** Samual Hayman, MBBS, MSc, FRACP; Janet Martin, BScPhm, PharmD, MSc; Kumar Sridhar, MD, MSc, FRCPC; J. David Spence, MD, FRCPC; Pallav Garg, MBBS, MSc, FRACP.

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**BACKGROUND:** Paradoxical embolism via patent foramen ovale has been implicated as a key mechanism in cryptogenic ischemic stroke. Randomized controlled trials of PFO closure versus medical therapy to prevent ischemic events have shown conflicting results. **METHODS:** Inclusion criteria were RCTs of PFO closure in cryptogenic stroke. The primary end point was ischemic stroke at long-term follow-up. Secondary end points included transient ischemic attack (TIA), death, serious adverse events and atrial fibrillation (AF). Sub-group analyses according to shunt size, medical therapy, and presence of atrial septal aneurysm (ASA) were performed. **RESULTS:** Five RCTs involving 3,630 patients were included. Fifty-five

percent were male. ASA was present in 32.2% and large shunt in 51.9%. PFO closure was associated with a reduction in recurrent ischemic stroke compared to medical therapy (OR 0.44, 95% CI 0.22-0.89, p=0.02). There was no difference in TIA (OR 0.80, 95% CI 0.53-1.19, p=0.26) or death (OR 0.75, 95% CI 0.35-1.59, p=0.45). PFO closure was associated with increased risk of AF (OR 5.16, 95% CI 2.01-13.2, p<0.001) but not serious adverse events (p=0.38) or bleeding (p=0.71). PFO closure was effective in reducing ischemic stroke in large shunts (OR 0.28, 95% CI 0.14-0.54, p<0.001) but not smaller shunts (p=0.55) or ASA (p=0.27). Benefit of PFO closure was seen versus antiplatelet therapy (OR 0.38, 95% CI 0.17-0.84, p=0.02) but not anticoagulation (p=0.65). **CONCLUSION:** PFO closure is effective in reducing recurrent ischemic stroke compared to medical therapy, with increased risk of atrial fibrillation.

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### **Sharing of equipment used for the preparation of controlled-release oral opiates for injection is associated with HIV transmission: a case control study.**

**Laura Ball, MPH,** Venner C BSc, Tirona RG PhD, Arts E PhD, Puka K HBSc, Speechley M PhD, Gupta K MD, Wong R BSc, Hallam B BSc, Wiener J BHSc, Koivu S MD and Silverman MS MD.

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**Objective:** To determine whether sharing of injection drug preparation equipment (IDPE; e.g. filters, cookers) used for a controlled-release opiate is associated with HIV transmission, as well as to examine the properties of controlled-release opiates that may promote IDPE sharing and HIV transmission. **Design:** A mix-methods study was conducted. A case control study examined risk factors for HIV-positive status among people who inject drugs (PWID), comparing 35 HIV-positive cases and 84 HIV-negative controls. A laboratory study measured residual hydromorphone controlled-release and immediate-release in IDPE following aspiration of drug solution in conditions replicating PWID use. Another laboratory study measured HIV viral persistence in IDPE in the presence of hydromorphone controlled-release and immediate-release. **Results:** Sharing IDPE

without sharing needles or syringes was associated with HIV-positive status (aOR=22.1; p<0.001). IDPE sharing was almost universal (100% HIV+, 94% HIV-) among PWID using hydromorphone-controlled release. 45% of hydromorphone controlled-release remained in the IDPE following initial injection, with no change after heating, whereas only 16% of immediate-release hydromorphone was retained. HIV reverse transcriptase activity and infectivity were preserved in IDPE in the presence of hydromorphone controlled-release but not immediate-release hydromorphone. Heating the IDPE rapidly inactivated HIV. Conclusions: Sharing IDPE is associated with HIV infection. Hydromorphone controlled-release preparation leaves significant drug residue, which could encourage IDPE sharing. Drug excipients preserve HIV viability, which could potentiate HIV transmission. Heating IDPE may be an effective harm reduction strategy.

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### **Leflunomide for the Treatment of Systemic Vasculitis.**

**Shorooq Banjar**, Dr. Lillian Barra.

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Background: Primary systemic vasculitis (SV) consists of rare autoimmune diseases characterized by inflammation of blood vessels. SV often leads to major organ damage with high mortality. Therapies to induce and maintain remission include glucocorticoids (GC), cytotoxic agents and immunosuppressants. Unfortunately, relapses with first-line maintenance therapies (GC, methotrexate and azathioprine) occur in 25-75%. Leflunomide (LEF) is an immunosuppressant commonly used in inflammatory arthritis. We aim to investigate the effectiveness of LEF in SV. Methods: Case series of all SV patients treated with LEF at the Interdisciplinary Vasculitis Centre (IVASC), St. Joseph's Health Care London. The diagnosis of SV, remission and relapse was defined based on clinical assessment, biomarkers, imaging and/or biopsy. Result: The study included 17 patients: median age was 70 (34-85) years and disease duration was 5 (3-20) years; 64% were females. Diagnoses were Giant Cell Arteritis (35%) or ANCA-associated vasculitis (65%). LEF was used for maintenance of remission or to treat non-

severe relapses based on patient preference or due to contraindications, adverse events or failure of other drugs. Median duration of treatment was 6 (2-65) months. We found that 13/17 (76%) treated with LEF achieved remission. Of these, 2 (14%) relapsed after 5 and 56 months. Four patients discontinued therapy due to adverse events: recurrent infections, diarrhea and neuropathy. Conclusions: LEF is an option in SV for maintaining remission or treating non-severe flares. However, severe adverse events can occur. This study supports the development of larger studies to determine LEF efficacy and safety for the treatment of SV.

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### **Differing Attending Physician Approaches and their Impact on Trainee Understanding of their Role During a Hospital Admission**

**Katherina Baranova**, Mark Goldszmidt.

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Background: In an earlier study, we had shown that while attending physicians universally focus on the acute problem, they further conceptualize the purpose of admission to hospital in three ways: overt focus on discharge efficiency (health stewardship); monitoring and management of chronic conditions; or improvement of overall health status (advocacy). This study further explores how these perspectives are signaled to the team and how trainees grapple with tensions between advocacy and stewardship. Methods: Participants included eight attending physicians, two junior attendings, ten senior medical residents, fifteen first year residents, and sixteen clinical clerks. Data was collected through direct observation and field interviews during 28 observation periods (approximately 150 hours) in two hospital clinical teaching units. Data collection and analysis occurred iteratively in keeping with constructivist grounded theory methodology. Results: While rarely made explicit, purpose of admission is reinforced through daily interaction with the attending. Following a transition, trainees begin to align their practices towards attending priorities – for instance, focusing on discharge barriers with attendings who prioritize discharge efficiency. Not infrequently, trainees experienced internal conflict in reconciling their own perspectives with

those of the attending. Strategies included advocating to the attending or working around them. Conclusion: Attending physicians' perceptions around purpose of admission play a powerful role in the hidden curriculum. The lack of overt dialogue around admission purpose can lead to mixed messages, dysfunctional collaboration, and lost educational opportunities for exploring the inherent tensions between the advocacy and stewardship roles.

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### **Emergency department performed renal point-of-care ultrasound (POCUS) for the assessment of obstructive uropathy: Accuracy and impact of a training curriculum and ongoing educational intervention.**

**Dr. David Bastien**, Dr. Drew Thompson, MD, Dr. Behzad Hassani, MD, Dr. Frank Myslik, MD, Jad Serhan, Kristine Van Aarsen, MSc.

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Hydronephrosis (HN) is the de facto measure for assessing obstructive uropathy and can be evaluated using renal Point-of-Care Ultrasound (POCUS) in the emergency department (ED). This study's aim was to implement a renal POCUS curriculum to test if quality assurance (QA) leads to improved interpretation of HN. A prospective crossover cohort study was used. Physicians were grouped into a QA or control group (NQA) and performed POCUS scans on patients requiring a formal renal US. The QA group received feedback on their assessment of HN using a defined objective grading system. Sensitivity and specificity was recorded comparing POCUS to a formal radiology report. At 10-weeks, QA and NQA groups were switched. Of the fourteen ED physicians that participated, 35.7% had at most 4 years post training experience and 28.6% had at least 15 years. Participants completed an introductory POCUS course and 92.3% felt not at all to somewhat comfortable using POCUS to assess HN. At time of submission, the first 10 weeks was complete and 36 and 27 POCUS scans were available in the QA and NQA group, respectively. Sensitivity and specificity were better in QA versus NQA group; however, differences did not reach statistical significance. (Sensitivity- 85.7%

vs 50.0%, 95% CI -15.2% to 72.6%, p=0.22; Specificity- 89.3% vs 73.9%, 95% CI -8.24% to 39.24%, p=0.16). Educational feedback given to ED physicians using POCUS showed improved sensitivity and specificity when assessing HN. Low sample size likely limits reaching statistical significance.

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### **High Dose Vitamin D3 to Improve Physical Performance in Frail Older Adults. A Feasibility Study.**

**Nick Bray**, Dr. Tim Doherty Dr. Manuel Montero-Odasso.

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Vitamin D deficiency is ubiquitous in frailty but the effect of vitamin D supplementation to improve outcomes in frail individuals is unclear. Doses much higher than the current recommended amount (800 IU/day) may be needed to have an effect on (pre)frail older adults. We hypothesized that 4000 IU/day of vitamin D3 would: 1) lead to an improvement in physical performance measures; and 2) be feasible and safe for a (pre)frail population. Upon waking, participants consumed 4000 IU of vitamin D3 and 1200 mcg of calcium carbonate every day for four months. Pre and post-intervention assessments were identical. A validated, operationalized version of the Fried/Cardiovascular Health Study criteria determined frailty status. Maximal handgrip and knee extension isometric contractions, gait velocity and the short physical performance battery (SPPB) protocol evaluated physical performance. Frail individuals exhibited a significant improvement in SPPB score (p = 0.005) and vitamin D serum levels (VDSL; p = 0.011). An additional sex stratification revealed a significant improvement in grip strength for females (p = 0.003). Individuals with insufficient baseline VDSL ( $\leq 75$  nmol/L) showed significant improvement in SPPB score (p = 0.04), VDSL (p =  $< 0.001$ ) and fast gait velocity (p = 0.004). Knee strength and VDSL exhibited a significant correlation (r=0.446, p = 0.006). No participants reported an adverse event. This pilot study demonstrates the feasibility and safety of high dose vitamin D supplementation. Furthermore, it provides results to calculate effect sizes for a definite randomized controlled trial to test the effectiveness of this intervention.

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### **Measuring GIM Consultation Skills in Longitudinal Training: a quantitative analysis of resident consultation letters**

**Dr. Zain Burhani, Dr. Saad Chahine, Dr. Noureen Huda.**

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**Background:** GIM training programs were implemented in Canada in 2012. A key outcome of GIM training is providing written consultations to family physicians. The key clinical experience for learning consultation skills is longitudinal rotations. To date, there are no studies looking at outcomes of GIM training in Canada or the influence of longitudinal training on developing consultation skills. The purpose of this study was to analyze consultation letters from GIM longitudinal rotations to determine if trainees are meeting outcomes of training, specific to written consultation skills. **Methods:** A previously validated consultation letter tool (Keely et al. 2007) was used to analyze 48 de-identified consultations notes from GIM longitudinal clinics. Letters were sampled across the following levels of training: entry into PGY-4, transition from PGY-4 to PGY-5 and end of training. Letters were rated by four physicians. Analysis of variance and interclass correlation were used to quantify the change in quality of letters from PGY-4 to PGY-5. **Results:** The consultation tool has 9 components. Preliminary analysis demonstrates that “focused and relevant history taking” and “relevant physical exam” are achieved early in training and maintained throughout training. “Brevity” and “clarity” in consultation are more challenging to master in training. Letters varied in achieving all nine components by end of training. **Conclusion:** Our preliminary results show that there is variation in quality of letters over training; some components are met early in training, while others were met inconsistently. Components that are met inconsistently may have implications for providing clear direction to consulting physicians.

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### **Telemetry: Are we overusing it? An analysis into the process of telemetry utilization at LHSC**

**Dr. Zain Burhani, Dr. Alan Gob.**

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**Background:** Telemetry is not a benign intervention. It is labor and resource intensive, costly, and can negatively impact patient care. The purpose of this study was to examine the process of telemetry utilization by CTU at University Hospital. **Methods:** Data was collected on patients admitted with telemetry to CTU teams over a 2 week period (n=35). Each patient’s chart was reviewed to determine their indication for telemetry, reason for continuation/discontinuation, and changes to management based on telemetry findings. We also documented if there were any admitted medicine patients in the ER waiting for telemetry packs. **Results:** The mean duration of telemetry was 2.83 days. There were six instances where patients were kept on telemetry for a prolonged period of time and 50% of those cases involved medical students as the primary caregiver. According to the AHA guidelines 17% of patients were classified as Class I, 37% as Class II and 46% as Class III. Telemetry changed management in only 2 out of the 35 patients (5.7%). At no point during the two week period was any patient admitted to medicine waiting for a telemetry pack in the ER. **Conclusion:** Almost half of our study population were low-risk Class III patients where telemetry is not indicated according to the AHA guidelines. In order to eliminate these inadequacies we propose a multi-pronged approach which include a guideline based protocol for telemetry initiation, nurse-managed telemetry discontinuation protocol, and education modules for trainees outlining an evidence based approach for the use of telemetry.

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## **Educational support around dialysis modality decision-making in patients with Chronic Kidney Disease (CKD): a qualitative study**

**Brendan P. Cassidy**, Lori Harwood, Leah E. Getchell, Michael Smith, Shannon L. Sibbald, Louise M. Moist.

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**Rational & Objective:** Patients with chronic kidney disease (CKD) are asked to choose a renal replacement therapy or conservative management. Education and knowledge transfer play key roles in this decision-making process, yet they remain a partially met need. We sought to understand the dialysis modality decision-making process through exploration of the pre-dialysis patient experience to better inform the educational process. **Study Design:** Observational descriptive study through qualitative semi-structured interviews. **Setting and Participants:** 12 patients with CKD at The Kidney Care Centre of London Health Sciences Centre on in-center hemodialysis, home hemodialysis or peritoneal dialysis. **Analytical Approach:** Conventional content analysis of the interview transcripts was utilized to analyze the data for common themes. **Results:** Three themes influenced dialysis modality decision-making: (i) Patient Factors: individualization, autonomy, and emotions; (ii) Educational Factors: tailored education, time and preparation, and available resources; and (iii) Support Systems: partnership with health care team, and family and friends. **Limitations:** Study population was largely well educated, Caucasian, with high health literacy. **Conclusions:** Modality decision making is a complex process, influenced by the patient's health literacy, values, environment and willingness to accept information. Patient education requires the flexibility to individualize the delivery of a standardized CKD curriculum in partnership with a patient-health care team, to fulfill the goal of informed, shared decision-making. **Keywords:** CKD, education, dialysis modality, informed decision-making, health care team.

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## **Does Trainee Participation Influence Adenoma Detection Rate During Colonoscopy?**

**Debarati Chakraborty MD**, Brian Yan MD, Michael Ott MD MSc, Cassandra McDonald, Mayur Brahmania MD MPH, Michael Sey MD MPH.

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**Background:** Screening colonoscopies reduce colorectal cancer, the second leading cause of cancer related mortality, by removing precancerous polyps. The most important marker of colonoscopy quality is the adenoma detection rate (ADR). Whether trainee involvement during colonoscopy affects ADR is unknown and the objective of this study. **Purpose:** To determine if trainee participation affects ADR during colonoscopies. **Methods:** A multi-centre prospective cohort study conducted using Southwest Endoscopy Quality Improvement and Performance Committee (SW-EQUIP) dataset within Southwest Regional Cancer Care Program of Cancer Care Ontario. Patients who underwent hospital based colonoscopy in Southwest Ontario between March 1st - December 31st 2017 included. We performed an interim analysis. Patient and procedure variables, including trainee involvement, patient age, gender, ASA score, indication, and bowel preparation quality were recorded by endoscopists prospectively and participation was mandatory. Pathology reports were manually reviewed to determine ADR. Crude analysis using chi square test performed to determine impact of trainee involvement on ADR. Multi-variable logistic regression conducted to control for potential confounders. **Results:** A total of 1303 patients underwent colonoscopy during the study period. Mean (SD) age was 59.5 years (14.6) and 55.5% were female. The majority of indications for colonoscopy were symptomatic patients (59.3%) followed by screening cases (37.5%). Conscious sedation was used 73.2% of the time and 80.9% had very good bowel preparation. 29.9% of cases had trainees involved and these patients were more likely to be older ( $p < 0.0001$ ), male ( $p = 0.004$ ) inpatients ( $p < 0.0001$ ), undergoing a screening procedure ( $p = 0.024$ ). On crude analysis, there was no difference in the ADR based on trainee involvement (21.0% non-trainee vs. 23.7% trainee,  $p = 0.29$ ). On multi-variable analysis, there was still no difference in the ADR based on

trainee involvement (OR=1.07, 95% CI 0.8-1.44, p=0.655). Only age (OR 1.03, 95% CI 1.02-1.04, p<0.001), and gender (OR=0.63, 95%CI 0.48-0.82, p=0.001) were associated with ADR. Conclusion: Trainee involvement did not significantly affect ADR during colonoscopy.

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### **CEBPD Acts as a Tumor Suppressor Gene in High-Grade Serous Ovarian Cancer**

**Rania Chehade**, Ramlogan Sowamber, Mahmoud Bitar, Omar L Nelson, Patricia A Shaw and Sophia HL George.

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High-grade serous ovarian cancer (HGSCs) remains the most fatal gynecologic malignancy accounting for the majority of ovarian cancer deaths and is associated with poor overall survival. There has been very little progress in the early detection, prevention and treatment of this highly deadly disease. Recently, the fallopian tube epithelium has gained recognition as the site of origin of HGSCs, highlighting an opportunity to understand early molecular events contributing to the carcinogenesis process. This is critical to support the development of targeted therapeutic approaches to improve outcome in HGSCs. C/EBP- $\delta$  represents a master regulator of gene transcription, commonly induced by stress and is associated with increased DNA damage. In a previous publication, we found C/EBP- $\delta$  to be among menstrual cycle regulated genes to be preferentially upregulated in the luteal phase of the menstrual cycle in fallopian tube epithelial cells and down regulated in HGSCs. Herein, we explored the 1) differential expression of C/EBP- $\delta$  in ovarian cancers 2) expression of C/EBP- $\delta$  in precursor lesions and 3) modeled the effect of over-expression of C/EBP- $\delta$  in an in vitro fallopian tube cell culture model. C/EBP- $\delta$  is down-regulated in over 60% of HGSC. C/EBP- $\delta$  protein expression exhibited a gradual decrease from the normal FTE to precursor lesions and lost in concomitant HGSC. In short-term cultures of FTE cell lines, over-expression of C/EBP- $\delta$  reduced 2D and 3D cell growth and contributed to a mesenchymal to an epithelial cell transition. The study highlights the role of C/EBP- $\delta$  as a potential tumor suppressor gene in HGSCs.

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### **Improving phosphate, calcium, and parathyroid hormone levels in hemodialysis patients: A quality improvement project**

J. Empringham, **H. Cheon**, C. Dai, D. Cheng, M. Cooper.

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Introduction: Phosphate, calcium, and parathyroid hormones (PTH) levels are difficult to manage in hemodialysis (HD) patients, predisposing them to mineral bone disease (MBD). Each patient often requires a unique combination of non-pharmacological, pharmacological, and surgical treatment options and their requirements change over time. Currently, treatment changes are often not explicitly documented in clinical notes, making it a challenge to assess specific treatment efficacies and failures. Objective: Improve the percentage of HD patients meeting target values for calcium, phosphate and PTH at University Hospital, using quality improvement methodologies. Methods: We adjusted a tracking form previously designed for peritoneal dialysis patients, which tracks treatment changes, and includes target ranges and suggested management for HD patients. A survey was then distributed to HD health care professionals to investigate baseline beliefs on this issue. The form was rolled out in February 2018, to be used with monthly bloodwork. Our primary outcome is the percentage of HD patients above target for phosphate and PTH levels. Further surveys and audits will follow. Preliminary Results: Baseline data revealed that 30% of HD patients are above target for phosphate and 20% above for PTH. The pre-survey was completed by health care professionals managing our patient cohort. 58% of responders felt that a well-defined structure around MBD management in HD patients is missing. Furthermore, 54% believed that lack of knowledge was a barrier in proper management. We expect our form will help elucidate trends and provide the necessary knowledge for proper treatment of MBD in HD patients.

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## **Microvascular Architecture and Cellular Phenotypes in Patients with Severe Peripheral Artery Disease**

**Jacqueline Chevalier**, John-Michael Arpino, Hao Yin, Caroline O'Neil, Jason Lee, Luc Dubois, Adam Power, Douglas Hamilton, J. Geoffrey Pickering.

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**BACKGROUND:** Peripheral arterial disease (PAD) is a major cause of morbidity and mortality. Bypass and stent procedures have a significant failure rate, possibly due to disease in the distal microvessels. However, little is known about microvessels in patients with severe PAD. I hypothesize that previously unidentified abnormalities exist within the microvascular network in patients with PAD. **METHODS:** Human skeletal muscle tissues were collected during below-knee leg amputation in patients with critical limb ischemia. Control muscles from the chest wall were harvested from patients undergoing cardiac surgery. Paraffin-embedded sections were stained with hematoxylin and eosin, and double-immunostained for CD31 and smooth muscle SM-alpha-actin. Frozen muscle 100 µm-thick sections were similarly immunostained, after which 3D confocal reconstructions were analyzed for arteriolar smooth muscle cell (SMC) wrapping patterns and network architecture. **RESULTS:** Regions of skeletal muscles were determined to be either necrotic (enucleated) or regenerating (central nuclei). There was a 4.3-fold increase in capillary density in the diseased muscles ( $p=0.0002$ ). Remarkably, double-labelling revealed that capillaries in regenerating muscle were excessively wrapped by SM-alpha-actin-positive cells (2.0-fold,  $p=0.0001$ ). Confocal reconstructions of complete arterio-venous units identified SM-alpha-actin-positive cell wrapping of entire capillary beds, suggesting arterio-venous shunting. In contrast, reduced SMC wrapping was found at the arteriolar level. As well, endothelial cells were swollen and impinged on the lumen, and there were arteriolar trifurcations, a violation of normal microvascular architecture. **CONCLUSIONS:** Skeletal muscles of patients with PAD demonstrated hyper-wrapped capillaries, and poorly wrapped and stenotic arterioles. These derangements could compromise oxygen delivery and lead to treatment failures.

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## **Median stroke response times at Grand River Hospital: Are we meeting the benchmarks?**

**Dr Genevieve Chick**, Dr Stephen Gilck.

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**Introduction:** With the implementation of new management strategies in the treatment of acute stroke, meeting the national benchmark times for (1) door to CTA (CT- angiography scan) (2) door to tPA (thrombolytic) and 3) door to EVT (endovascular therapy) are becoming increasingly more important for patient outcomes. This study aims to quantify our stroke data at Grand River Hospital, and to implement policies to improve our patient care in this field. **Methods:** Our study is a retrospective review of these three key time indices [(1) to (3)] in the charts of 89 patients who were triaged in the emergency department at Grand River Hospital as an acute stroke. We compared these times to the benchmark times as per the Canada Stroke Best Practices. **Results:** In this study, 115 charts were audited between September 15, 2017 and December 24, 2017. The median time for door to CT scan was 14 minutes (benchmark time is within 15 minutes); door to CTA was 92 minutes (benchmark within 15 minutes); door to tPA was 40 minutes (benchmark within 30 minute); door in to door out for EVT was 79 minutes (benchmark time is 45 minutes). **Conclusion:** At Grand River Hospital, in the acute care stroke setting, a focus on improving the median times for CT, CTA, tPA and EVT is integral. The next step in our project will be following another 6 months of stroke data at our center, and subsequently implement quality improvement processes to improve overall patient care in this area.

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## **Does Immunosuppression Slow Disease Progression in Primary Sjogren's Syndrome?**

**Lu Lucy Chu**, Kathy Cui, Janet Pope.

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**Introduction**The current focus of treatment in primary Sjogren's Syndrome (pSS) is mainly symptomatic management. Since pSS is an autoimmune disease with multi-system involvement, there may be a role for systemic immunosuppression to prevent progression. **Methods**Five electronic databases (MEDLINE, EMBASE, CENTRAL, CLINICALTRIALS.GOV, WHO ICTRP) were searched to include relevant RCTs. Main efficacy measures included ocular dryness, oral dryness, tear production, salivary flow, and ESR/CRP; Safety measures included serious adverse events (AEs) and withdrawals due to AEs. **Results**The searched yielded 32 trials evaluating 19 different medications. Average duration of diagnosis up to 9.2 years. Twenty-two trials examined ocular and oral dryness, of which only 2 and 3 revealed statistically significant improvements respectively. No studies found benefit for tear production; 3/16 studies and 2/14 studies found improvements in unstimulated and stimulated salivary flow respectively. Reductions in ESR were seen in 3/14 studies. Many other small studies noted trends toward improvement, but no particular drug consistently had adequate power to demonstrate statistical benefit in subjective or objective measures. Meta-analysis was thus performed at 6 months. Statistically significant improvements as compared to placebo were seen for the following three outcomes: unstimulated salivary flow ( $p=0.003$ ), stimulated salivary flow ( $p=0.02$ ), and ESR ( $p<0.001$ ). However, there were also increased withdrawals from AEs (RR 2.33;  $p=0.03$ ). **Conclusion**Combining the findings of small-scale studies show that reducing inflammation improves salivary gland function in pSS. Further work is needed to establish outcomes reflective of disease activity as opposed to damage.

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## **Frailty and Hospitalization in Dialysis: Evaluation of the Clinical Frailty Scale.**

**David Clark**, Kara Matheson, Amanda Miller, Bryce Kiberd, Arsh Jain, Karthik Tennankore.

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**Background:** Dialysis patients are frequently hospitalized. Prior studies have not considered frailty severity as a predictor of hospitalization. **Objectives:** To determine if there is an association between frailty severity and hospitalization among incident dialysis patients. **Methods:** A retrospective cohort study of adult dialysis patients within the Nova Scotia renal program from 1 Jan 2009 - 31 Dec 2015 (last follow-up 1 July 2016). The Clinical Frailty Scale (CFS) score was determined for patients at dialysis initiation and allocates a single point to different states of frailty (1, fit - 7, severely frail). Cumulative time admitted (days admitted/total days at risk), and hospitalization rate (admissions/year) was determined for the entire cohort and selected CFS categories. The incident rate of admission for each one-unit increase in CFS-score was determined and by CFS-category. **Results:** Among 647 patients (CFS<4; N=251, CFS 5-6; N=235, CFS 6-7; N=78) initiated on dialysis, an average of 38 +/- 66 days was spent admitted to hospital during the study period. Moderate-severely frail patients (N=78; CFS 6-7) averaged the most hospital admissions/year (2.64 + 2.24) and highest (6 + 11%) cumulative time admitted. Adjusting for time between admissions, the incidence rate for hospitalization was 1.39 (95% CI [1.17-1.65]) times higher for the frailest patients (CFS 6-7) compared to less frail (CFS<4). The percent increase change in the incident rate of hospital admission was 11% for every unit increase in CFS-score (IRR 1.11, 95% CI [1.06 - 1.15]). **Conclusions:** A higher severity of frailty at dialysis initiation is associated with a higher hospitalization rate.

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## **Outcomes of out-of-hospital cardiac arrest in London, Ontario**

**Michael Clemente, MD**, Karen Woolfrey, MD, FRCPC; Kristine Van Aarsen, MSc; Melanie Columbus, PhD.

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**Introduction:** Out of hospital cardiac arrest (OHCA) continues to carry a very high mortality rate, with approximately 10% surviving to hospital discharge. We sought to determine if outcomes from out of hospital cardiac arrest (OHCA) at our centre were consistent with recently published North American outcomes data. **Methods:** We performed a retrospective analysis (Sept 2011 – June 2015) of the Resuscitation Outcomes Consortium database, which contains pre-hospital, in-hospital and outcomes data on adult, EMS-treated, non-traumatic OHCA. Patients under 18 years, with missing age data or with obvious non-cardiac causes of arrest were excluded. **Results:** During the study period, there were a total of 997 OHCA; 86 met exclusion criteria. Of the 911 remaining patients, 557 (61.1%) were transported to hospital. 92 (35.1%) were receiving ongoing CPR at the time of their presentation to the ED. Of those transported to the ED, 262 (47.0%) achieved sustained ROSC, defined as survival to ED discharge. A total of 95 patients survived to hospital discharge, 10.4% of all OHCA. Of those who survived to hospital discharge who had neurologic outcome data, 90.5% had a modified Rankin score of  $\leq 2$ . Initial presenting rhythm was VF or pulseless VT in 233 patients and PEA or asystole in 636 patients. Respectively, transport to the ED occurred in 91.0% and 50.3%, sustained ROSC was achieved in 57.3% and 18.1%, and survival to hospital discharge was achieved in 30.5% and 2.7%. **Conclusion:** Outcomes from out of hospital cardiac arrest in London, Ontario are comparable to other sites across North America.

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## **Post-return of spontaneous circulation care and outcomes – a single centre experience**

**Michael Clemente, MD**, Karen Woolfrey, MD, FRCPC; Kristine Van Aarsen, MSc; Melanie Columbus, PhD.

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**Introduction:** In 2015, the AHA released updated guidelines in post-return of spontaneous circulation (ROSC) care, advocating for more liberal utilization of emergent coronary angiography. We sought to investigate how frequently emergent angiography was utilized at our centre, and its effect on outcomes. **Methods:** We performed a retrospective analysis (Sept 2011 – June 2015) of the Resuscitation Outcomes Consortium database. Key variables included rates of post-ROSC emergent angiography, survival to hospital discharge and survival to hospital discharge with favourable neurologic outcome (modified Rankin score  $\leq 2$ ). **Results:** During the study period, there were a total of 997 OHCA; 86 met exclusion criteria. Of the 911 remaining patients, 557 (61.1%) were transported to a local ED. Of those transported to the ED, 262 (47.0%) achieved sustained ROSC, defined as survival to ED discharge. Of those who achieved sustained ROSC, ECG interpretation data was available on 214 patients, of whom 56 had definite STEMI, and 135 had definite absence of STEMI. 37/56 (66.1%) definite STEMI patients and 58/262 (22.1%) of patients overall received coronary angiography within 24 hours of presentation. Of those 58 patients, 38 (65.5%) underwent percutaneous coronary intervention. Of post-ROSC patients who received emergent coronary angiography compared to those who did not, 40/58 (69.0%) versus 55/204 (27.0%) survived to hospital discharge, and 37/58 (63.8%) versus 18.8% survived with good neurologic outcome. **Conclusion:** Only 22.1% of patients with OHCA, and only 66.1% with ECG-proven STEMI underwent emergent coronary angiography post-ROSC. Further investigation into causes for delay or the withholding of emergent angiography is necessary.

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### **Extended Screening Costs Associated With Selecting Donors for Fecal Microbiota Transplantation for Treatment of Metabolic Syndrome-Associated Diseases**

**Laura Craven**, Seema Nair Parvathy, Justin Tat-Ko, Jeremy Burton, and Michael Silverman.

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Background: Knowledge of the impact of the gut microbiome on conditions other than Clostridium difficile infection has been rapidly increasing, and the list of diseases that may be treated by fecal microbiota transplant (FMT) is expanding. The need to exclude donors with an increased risk of these diseases has left uncertainties regarding the cost and feasibility of donor screening. The aim of this study was to compare our experience to other donor-screening programs and report the costs associated with establishing this program, for the treatment of metabolic syndrome-related conditions. Methods: Forty-six potential donors (PDs) had their medical histories and physical examinations undertaken by a physician. Blood, stool, and urine were screened for 31 pathogens in addition to biochemical characteristics. The price of advertising, doctor's visits and diagnostic tests were calculated to determine the cost of finding a donor. Results: 5 of 46 PDs passed the history, examination, blood, stool, and urine tests. The most common reasons for exclusion included a BMI >25 or the detection of Blastocystis hominis, Dientamoeba fragilis, or Helicobacter pylori. Four of five eligible donors had subsequent travel or illness that contraindicated donation, so only 1 PD was suitable. The total cost for finding a single suitable donor was \$20,250. Conclusions: New potential therapeutic uses for FMT have created a demand for stricter exclusion criteria for donors. This study illustrates that screening many individuals to find a donor and the subsequent associated costs may make central processing and shipment a more reasonable alternative.

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### **What are the Optimal Long-Term Storage Conditions for Donor Samples Used in Fecal Microbiota Transplantation?**

**Laura Craven**, Greg Gloor, Gregor Reid, Michael Silverman, Jeremy P. Burton.

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Background: There is currently a lack of standardization by fecal microbiota transplantation (FMT) clinics to store and prepare fecal samples for transplant. These methods likely influence the number and composition of viable bacteria delivered during treatments, potentially making FMTs less effective. Traditional next-generation sequencing amplifies DNA from both live and dead bacteria. Propidium monoazide (PMA) can be used to bind DNA from dead bacterial cells and prevent its amplification, only allowing the DNA from live bacterial cells to be analyzed. The aim of this study was to deduce what storage conditions for donor stools resulted in the highest bacterial viability. Methods: Fecal samples were suspended in either water, saline, 10% glycerol or remained as whole stool. For each suspension fluid, the samples were stored at 4 °C for 1 week, -20 °C or -80 °C for 3 months. At each time point a portion of the sample was used to culture the viable bacteria, the cells were treated with PMA and the DNA was extracted for 16S rRNA gene sequencing analysis. Results: Storage in 10% glycerol and whole stool resulted in the highest viability and there were no changes in bacterial viability after 3 months. Conclusions: Stricter regulations on the preparation and storage conditions for stool samples need to be developed and practiced. Ideally, fecal samples for FMT should be stored as whole stool or suspended in glycerol at -80 °C for long-term storage and should be used within 3 months.

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### **Can Dual-Task Gait Assessment Differentiate Cognitive Impairment Subtypes in a Clinical Setting?**

**Stephanie Cullen**, Michael Borrie, Susan Carroll, Manuel Montero-Odasso.

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Background: Gait velocity has been shown to decline along with cognitive function. Recently,

dual-task gait (walking while performing a cognitive demanding task) has been linked to increased risk for progression to dementia in older adults with MCI. However, most of these findings come from research environments and many clinics do not currently use gait testing as a complement to cognitive assessments. Objective: We aimed to examine whether patients from a memory clinic show differences in dual-task gait based on their cognitive diagnosis (SCI, MCI, or dementia). Methods: Patients in the Aging Brain and Memory clinic performed a usual gait walk and three dual-task walks: counting backwards by ones, counting backwards by seven (serial sevens), and naming animals. One-way ANOVA and General Linear Models were performed to evaluate gait velocity and dual-task cost (DTC, %) across groups. Results: 178 patients were assessed with cognitive diagnosis of SCI (n=40), MCI (n=72), or dementia (n=66). Performance in single and dual-task gait declined across the cognitive spectrum showing that as the cognitive impairment increased, gait performance showed slower gait velocity (single gait,  $p<0.001$ ; counting gait,  $p<0.001$ ; naming animals,  $p<0.001$ ; serial sevens,  $p=0.015$ ) and higher dual-task cost (naming animals,  $p=0.037$ ; counting gait,  $p=0.037$ ). Conclusion: Our results show that gait velocity can be a powerful identifier of cognitive decline. These results align with previous research that has shown a decline in dual-task gait velocity with declining cognitive function. Further studies may determine if incorporating dual-task gait testing in clinics can help predict cognitive decline.

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### **Anti-IL-12/23p40 antibodies for maintenance of remission in Crohn's disease**

**Sarah C Davies**, Tran M Nguyen, Claire E Parker, John K MacDonald, Vipul Jairath, Reena Khanna.

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Background: Ustekinumab (CNTO 1275) is a monoclonal antibody targeting the standard p40 subunit of cytokines interleukin-12 and interleukin-23 (IL-12/23p40), which is involved in the pathogenesis of Crohns disease. Objectives: To assess the efficacy and safety of anti-IL-12/23p40 antibodies for maintenance of

remission in Crohns disease. Methods: A comprehensive search of multiple databases through September 2016 was completed. Randomized controlled trials (RCTs) in which monoclonal antibodies against IL-12/23p40 were compared to placebo in adults with active Crohns disease were identified for inclusion. Results: Two RCTs (n=542) met the inclusion criteria. One study (n=145) compared ustekinumab to placebo for 22 weeks. There was no difference in remission rates in this study (RR=0.80, 95% CI=0.63-1.02). However, ustekinumab was superior to placebo in rates of clinical response (RR=0.53, 95% CI=0.36-0.79). The other included study (n=259) compared ustekinumab administered every 8 weeks and 12 weeks to placebo for 44 weeks. Ustekinumab was superior to placebo in maintenance of remission and clinical response when administered every 8 weeks (RR=0.73, 95% CI=0.58-0.92 and RR=0.73, 95% CI=0.56-0.94) and every 12 weeks (RR=0.80, 95% CI=0.65-0.99 and RR=0.75, 95% CI=0.58-0.97). Data pooled from both studies showed there was no differences in incidence of adverse events (AE) or serious adverse events (SAE) (RR=0.94, 95% CI=0.86-1.03 and RR=0.69, 95% CI=0.42-1.15). Conclusions: Ustekinumab is effective for maintenance of clinical remission and response. There was no increased risk of AEs or SAEs. Ustekinumab is a promising new therapy for maintenance of remission in Crohns disease.

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### **Biometric Measurements of Hand Size in Patients with Acromegaly and Patients with Non-functioning Pituitary Tumors**

**S. De Brabandere**, P. Pobebe, A. Azzola, J.S. Milner, J. Mahon, D. W. Holdsworth, S. Van Uum.

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Introduction: Acromegaly is a rare and chronic progressive disease characterized by increased hand and ring size and overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Diagnosis is usually made 5 to 10 years after onset of symptoms. This study explored biometric hand size measurements of scanned copies of hands as a potential screening tool for earlier diagnosis of acromegaly. Method: We recruited 20 patients aged 18 and older; 10 had acromegaly (ACRO) and 10 had a non-

functioning pituitary adenoma (NFPA) and a normal IGF-1 level, with 5 men and 5 women in each group. We obtained scan copies of both hands. We developed a software program to analyze the palm surface area, palm diameter and finger diameters in both hands. We present data on the right-hand palm surface area comparing ACRO and NFPA specified for sex. Group results were compared using the t-test. Results: There was no statistically significant difference in age, BMI or IGF-1 levels between groups. For male patients, the right palm surface area was  $11020 \pm 371.9$  mm<sup>2</sup> in the ACRO group vs  $9951 \pm 175.3$  mm<sup>2</sup> in the NFPA group ( $P < 0.01$ ). For female patients, results for the right palm surface area were  $8093 \pm 253$  mm<sup>2</sup> in ACRO vs  $7234 \pm 280.9$  mm<sup>2</sup> in NFPA ( $P = 0.05$ ). Conclusions: Biometric hand size parameters obtained using scan copies of hands are significantly increased in ACRO compared to NFPA. Further studies are needed to determine if biometric hand size measurement may be a screening tool for earlier diagnosis of acromegaly.

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### **Lower 90-day hospital readmission rates for esophageal variceal bleeding in patients receiving TIPS: a nationwide linked analysis**

**Navjot Deol** and Barret Rush, Anour Teriyaki MD FRCPC, Michael Sey MD MPH FRCPC, Vipul Jairath MD PhD, Keith R Walley MD FRCPC, Leo A Celi MD MPH MS, Mayur Brahma MD MPH FRCPC.

**Objective:** Hospital readmission following a transjugular intrahepatic portosystemic shunt (TIPS) insertion after an episode of esophageal variceal bleeding (EVb) has not been well studied. We aimed to address this gap in knowledge. **Methods:** The Nationwide Readmission Database (NRD) was used to study the readmission rates for patients with decompensated cirrhosis who had a TIPS insertion performed for EVb. A propensity score matching model was created to match patients who received TIPS to those who did not. **Results:** A total of 42,679,001 hospital admissions from the 2012-2014 NRD sample were analyzed. There were 33,934 patients with

EVb who met inclusion criteria for the study, of which, 1,527 (4.5%) received TIPS after EVb. They were matched to 1,527 patients with EVb who did not undergo TIPS. With a uniform follow-up of 3 months, patients with TIPS were less likely to be readmitted with recurrent EVb (3.0%; 95% CI: 2.0-3.9 TIPS vs 9.3%; 95% CI: 7.6-11.0 no TIPS:  $p < 0.01$ ), although were more likely to be readmitted with HE (13.0% TIPS vs. 8.2% no TIPS:  $p < 0.01$ ). At 3 months, there was no difference in all cause hospital readmission rate (38.8%; 95% CI: 38.1-44.9 TIPS vs 41.5%; 95% CI: 34.1-43.3 no TIPS:  $p = 0.17$ ). **Conclusion:** In this large nationally representative study patients who underwent TIPS insertion after an episode of EVb had a significantly lower risk of 3-month readmission for recurrent EVb than those who did not receive TIPS although overall readmission remained unchanged.

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### **Identifying the genetic basis of vascular cognitive impairment using a custom designed next-generation sequencing-based gene panel**

**Allison A. Dillio**, Sali M. Farhan, Adam A. McIntyre, John F. Robinson, Donna Kwan, Rick Swartz, Ayman Hassan, Dar Dowlatshahi, Demetrios Sahlas, Gustavo Saposnik, Jennifer Mandzia, Leanne Casaubon, Michael J. Strong, Mario Masellis, Dennis E. Bulman, Ekaterina Rogava, Robert A. Hegele, ONDRI Investigators.

Vascular cognitive impairment (VCI) is characterized by cognitive decline resulting from stroke or cerebrovascular accident and is the second most common form of dementia, following Alzheimer's disease (AD). Approximately 30% of individuals who have experienced a stroke develop VCI. The Ontario Neurodegenerative Disease Research Initiative (ONDRI) is a province-wide, observational cohort study characterizing five neurodegenerative diseases, including VCI. The ONDRI genomics subgroup's objective is to elucidate the genetic landscape of these diseases. Particularly, in those with VCI we are interested in identifying genetic markers placing individuals at risk for developing cognitive impairment post-stroke. A custom next-generation targeted resequencing panel,

ONDRISeg, was designed to target 80 genes previously associated with the neurodegenerative diseases of interest. We analyzed sequencing data with custom bioinformatics workflows and manual curation to identify candidate variants likely to be disease causing for each participant. The VCI cohort consists of 161 participants with a mean age of 70.2±7.5 years; 31.6% are female. Across the cohort, 255 unique non-synonymous rare variants were identified of possible clinical significance, with 86% of individuals harbouring at least one. Interestingly, 12.5% of the unique variants occur in genes previously associated with VCI or related cerebrovascular phenotypes. Analysis of rare variant burden is ongoing, including comparisons with age-matched controls and association analysis with age of onset, degree of cognitive impairment, and other clinical measures. This work will allow for the identification of genetic biomarkers associated with VCI onset, progression, and outcomes, providing important early-diagnosis tools and possible therapeutic targets.

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## Large-scale deletions of the *ABCA1* gene in patients with hypoalphalipoproteinemia

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Large-scale deletions and insertions, namely, copy-number variation (CNVs) have been studied in the context of lipid phenotypes and dyslipidemias, such as familial hypercholesterolemia, but have not been considered for extremes of high-density lipoprotein (HDL) cholesterol. We screened our collection of patients with low HDL cholesterol for

CNVs disrupting genes consistent with the phenotype, such as *ABCA1*, *APOA1*, and *LCAT*. CNVs were detected using the VarSeq-CNV® caller algorithm, which relies on sequencing depth of coverage for analysis; we applied this algorithm to the sequencing data that had been generated previously by our targeted next-generation sequencing panel, LipidSeq. We identified three individuals who carried three unique deletions in *ABCA1*: a heterozygous deletion of exon 4, a heterozygous deletion spanning exons 8-31, and a heterozygous deletion of the entire *ABCA1* gene. Breakpoints were confirmed for the smaller two deletions using Sanger sequencing, and the full-gene deletion was confirmed using the Affymetrix CytoScan™ HD Array. Given the role of the *ABCA1* transporter in reverse cholesterol transport, large-scale disruptions of the gene likely lead to the protein's loss of function, in which cholesterol efflux from macrophages is decreased, and the number of circulating HDL particles decreases as a result. This screening exercise serves as a proof-of-concept regarding this novel method of CNV identification using next-generation sequencing data in dyslipidemia patients—specifically, those with extremely low HDL cholesterol. This is the first example of *ABCA1* CNVs in patients with hypoalphalipoproteinemia. While the prevalence of CNVs was low, our findings emphasize the genetic complexities underlying deviations in HDL cholesterol levels, and the value in considering large-scale variation when studying the genetic basis of extreme HDL cholesterol levels.

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## A Comparison of Patient and Physician Reported Onset in Early Rheumatoid Arthritis

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*Objective:* To compare patient versus physician reported timing of early rheumatoid arthritis (RA) onset in a large multi-centre incident RA cohort. *Methods:* Data were from 2683 patients with early/suspected RA (persistent symptoms <1

year) from the Canadian Early Arthritis Cohort (CATCH). Patients completed baseline questionnaires asking symptom onset timing. Rheumatologists completed questionnaires for earliest persistent synovitis. Descriptive statistics summarized symptom onset distributions. Spearman's and intraclass correlation coefficients assessed correlation and agreement in onsets. Groups with concordant timing versus discordant timing of 30 days or more were compared for prognostic factors using ANOVA, and regression analysis identified predictors of discordance. *Results:* Median patient symptom duration (IQR) was 178 days (163), physician-reported duration was 166 (138), and median difference was 0 (0). There was a strong, positive correlation between patient and physician-reported onset ( $r=0.751$ ,  $p<0.001$ ), while agreement was low ( $ICC=0.076$ ,  $p=0.02$ ); 1940 (72.3%) patients had similar patient and physician symptom onset (<30 days), whereas 497 (18.5%) patients reported onset 30 or more days preceding physicians, and 246 (9.2%) 30 or more days after physicians. Patients reporting onset preceding physicians were more likely to have lower baseline DAS28, swollen joint counts and ESR ( $p<0.05$ ). Patients reporting onset after physicians were more likely to be rheumatoid factor positive ( $p<0.05$ ). Regression showed osteoarthritis, fibromyalgia, and smoking predicted greater discordance in onset. *Conclusion:* These differences are important as the chance of remission is best in early disease and it is important to know the timing of disease onset and by whose perspective.

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### **IgG4-related disease in a teaching hospital in Ontario**

**Andreu Fernandez-Codina**, Janet E Pope, Lillian Barra.

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**Background:** IgG4-related disease (IgG4-RD) is a rare systemic autoimmune disease characterized by fibrosis and inflammation. In Canada, it has been more frequently described in Asian individuals living in British Columbia. **Objectives:** To describe the epidemiological and clinical characteristics, as well as the treatment outcomes in a population of IgG4-RD patients in London, Ontario. **Methods:** Patients included met

almost one of the available diagnostic criteria: the 2012 international pathology consensus or the 2011 Japanese comprehensive criteria. A clinical chart review was performed, including patients from December 2017 to January 2018. Outcomes were assessed by the original version of the IgG4 responder index (RI) and a version without the serum IgG4 domain. **Results:** Five patients were included. Four (80%) were female, mean age 49 years. Four patients had Caucasian ascent (80%), and 1 North African/middle-East (20%). Four individuals (80%) had systemic IgG4-RD involving more than 1 tissue. The involved tissues were: paranasal sinuses (3), lung (1), pachymeninges (1), skin (1), lacrimal glands (1), orbit (1) and lymph nodes (1). Only 3 patients had serum IgG4 determinations, and in 2 it was elevated ( $>86.6$  mg/dL). All patients received glucocorticoids. Two received methotrexate and azathioprine directly as maintenance drugs. Another patient had methotrexate added after a flare. Two more patients required treatment with rituximab due to persistent activity. **Conclusions:** In contrast with the series from Vancouver, our patients (limited sample) were predominantly Caucasian and female. IgG4-RD tended to have multiorgan involvement. Glucocorticoids were the main treatment, followed by immunosuppressive agents in some cases.

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### **Phantom Cushing's: Where's the Cortisol?**

**Chris Foster**, David McCormack, Stan Van Uum.

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**BACKGROUND:** Therapeutic glucocorticoids can cause iatrogenic Cushing's syndrome, though this is rare with inhaled steroids. Medications that interfere with steroid metabolism through inhibition of CYP3A4 may increase this risk. **CASE:** A 57-year-old woman presented with a one year history of weight gain, peripheral edema, and moon facies. She had a history of asthma and recurrent pneumonia caused by *Aspergillus fumigatus*. Her Cushingoid appearance was discordant with lab values including morning serum cortisol  $< 28$  (normal 135-537) nmol/L, urine free cortisol  $< 28$  ( $< 275$ ) nmol/day, and ACTH 0.5 ( $< 14.0$ ) pmol/L. An MRI pituitary revealed no abnormalities. A medication interaction was identified as the cause. She used

a budesonide/formoterol puffer daily for her asthma and had recently required long courses of itraconazole for Aspergillus pneumonia flares. By inhibiting CYP3A4, itraconazole allowed budesonide, a potent inhaled glucocorticoid, to reach high systemic levels while eluding detection in cortisol assays. The patient later began a hydrocortisone taper for secondary adrenal insufficiency. However, another episode of Aspergillus pneumonia necessitated further itraconazole, complicating this process. Hair cortisol analysis may help quantify her steroid exposure during this period. **DISCUSSION:** This case highlights an important interaction between two medications often used together in the management of Aspergillus lung disease. This interaction can increase the risk of Cushing's syndrome despite low cortisol results. It is challenging to identify and quantify biochemically, and complicates steroid dose adjustment/tapering. Physicians should monitor these patients closely for iatrogenic Cushing's syndrome and interpret clinical and biochemical findings carefully.

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### **Regulation of NK Cell Cytotoxicity by TEC Expression of Clr Proteins in Kidney Ischemia Reperfusion Injury (IRI)**

**Benjamin Fuhrmann**, James Yip, Dameng Lian, Shenqwu Ma, Zhuxu Zhang, Anthony M. Jevnikar.

Kidney tubular epithelial cells (TEC) may negatively regulate NK cell activation and cytotoxic capacity by surface expression of a novel class of C-type lectin-related ligand proteins (Clr) which may be exploited to prevent ischemia reperfusion and alloimmune transplant injury. Expression of Clr-b/-f was confirmed in wild type (WT) and transformed mouse TEC using RT-PCR. TEC were treated in vitro with Clr-b and -f siRNA, and silencing was confirmed by RT-PCR and flow cytometry. Cell death was measured in NK-TEC co-cultures by target cell <sup>51</sup>Cr release. Clr-b and -f were expressed by WT TEC and upregulated by TNF $\alpha$ +IFN $\gamma$  in vitro. Clr-b surface expression was increased for >48hr in B6 kidneys following IRI. Elimination of either Clr-b or Clr-f by TEC did not increase NK mediated killing. However, simultaneous silencing of both

Clr-b and Clr-f expression resulted in increased NK killing of TEC compared to silenced Clr-b or Clr-f TEC (p<0.01), or WT control TEC (p<0.001). TEC may increase their expression of Clr-b/-f with ischemia and alloimmune renal injury as an endogenous mechanism of protection from NK cells during inflammation. As no current drugs target NK cells effectively, Clr-b and Clr-f fusion proteins that bind to NK cells bearing NKRP1 receptors may represent a novel strategy to protect organs from diverse forms of NK mediated inflammation and cytotoxicity.

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### **Mitochondrial membrane permeability plays a critical role for endothelial cell necroptosis and cardiac allograft rejection**

**Ingrid Gan**, Xuyan Huang, Jifu Jiang, Dameng Lian., Winnie Liu, Aaron Haig, Anthony M. Jevnikar, Zhu-Xu Zhang.

Transplant injury is invariably associated with programmed cell death resulting in delayed graft function and organ rejection. Many forms of PCD have been described including apoptosis, pyroptosis, ferroptosis, and necroptosis. We were the first to describe receptor-interacting serine/threonine protein kinase 3 (RIPK3) mediated necroptosis in transplant injury, where tissue necrosis and graft rejection were attenuated in RIPK3 null kidney and heart allografts following transplantation. Until now, the effect of mitochondrial dysfunction in the necroptotic pathway remains controversial – it is suggested that mitochondrial dysfunction may promote necroptosis in some studies but not in others. Here, our goal was to determine if mitochondrial dysfunction participates in cardiac cell necroptotic death and accelerates graft rejection. We found that TNF $\alpha$  triggered cells to undergo RIPK1- and RIPK3-dependent necroptosis under caspase-8 inhibition. Interestingly, inhibition of MPT could also inhibit cell necroptotic death. Deficiency and RNA silencing of MPT regulator protein cyclophilin-D (Cyp-D) protected MVEC from necroptosis. In vivo, Cyp-D deficient cardiac allografts showed prolonged survival in allogeneic BALB/c mice compared to wild type C57BL/6 grafts post transplantation. Our studies show that MPT may



be an important mechanistic mediator of necroptosis in MVECs, and targeting mitochondria-mediated cell death to reduce cardiac graft rejection has therapeutic potential.

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### **Serum adalimumab levels correlate with Crohn's disease severity**

**Mandark Gandhi**, Nilesh Chande, Larry Stitt, Jamie Gregor.

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**INTRODUCTION:** Patient factors do not factor into Adalimumab's dosing regimen. Guidelines, advocate monitoring trough drug levels to guide management in patients with suboptimal control. We aim to evaluate whether serum adalimumab levels correlate with Crohn's disease severity. Additionally, we aim to see if clinical and biochemical markers can be used as a surrogate for adalimumab levels. **METHODS:** A cross-sectional study was performed on Crohn's disease patients that had a measured adalimumab level. One hundred forty-nine patients were identified between January 2015 and August 2017. Disease severity was determined using the Harvey-Bradshaw Index (HBI). **RESULTS:** Out of 149 patients, 100 were in remission. Mean trough adalimumab level was 8.7µg/mL and 6.5µg/mL for remission and active disease groups respectively. Patients in remission had a mean weight of 78.4kg compared to 101.4kg in patients with active disease. Serum adalimumab levels correlated with HBI, weight and log CRP. The respective pearson correlation coefficients were  $r = -0.19$  ( $p=0.018$ ),  $r = -0.24$  ( $p=0.005$ ),  $r = -0.40$  ( $p=0.0004$ ). There were no statistically significant correlations between trough adalimumab level and albumin. Nor were there any significant correlations between HBI and weight, albumin or log CRP. Similar results were seen when stratified based on weekly ( $n=32$ ) or biweekly dosing ( $n=117$ ). **CONCLUSION:** Higher trough adalimumab levels correlated with lower disease activity, lower weight and lower CRP in patients with Crohn disease. Patients with higher disease burden and increased weight may benefit from empiric weekly dosing of adalimumab. These results lend support for increasing adalimumab dosing in non-responders.

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### **Direct Oral Anticoagulants for Thromboprophylaxis in Orthopedic Surgery: A Systematic Review of Population Based Studies**

**Alejandro Garcia-Horton, MD**, Fatimah Al-Ani, MD, MRCP and Alejandro Lazo-Langner, MD, MSc.

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**Objective.** Assess the efficacy and safety of DOACS in the prevention of thromboembolism in patients undergoing orthopedic surgery (OS) in population-based studies outside the framework of clinical trials. **Methods.** A systematic review of observational studies was conducted assessing the safety and efficacy of DOACs in patients undergoing OS. Efficacy outcomes included VTE and safety, including major bleeding (MB), gastrointestinal (GI), central nervous system (CNS) bleeding, and bleeding-related deaths. We conducted a meta-analysis of proportions using both fixed and random effects models. **Results.** Ten articles published between 2012 and 2016 were included. Of those 10 studies, 9 assessed rivaroxaban, 1 dabigatran, and none assessed apixaban. The analysis included rivaroxaban studies only. The total number of evaluable participants was 27,158 for VTE and 27,130 for MB. Studies assessing rivaroxaban in patients undergoing OS showed a VTE rate of 0.8% [95%CI: 0.73-0.95] (fixed) and 1.6% [95%CI: 1.39-1.79] (random). The MB rate with rivaroxaban was 0.7% [95%CI: 0.61-0.81] (fixed) and 2.2% [95%CI: 2.04-2.46] (random). The bleeding related mortality was reported in 3 studies ( $n=1,250$ ) and found to be extremely low: 0.05% [95%CI: 0.0-0.39] (fixed) and 0.08% [95%CI: 0.01-0.45] (random). **Conclusion.** In "real life", the main DOAC used for VTE prophylaxis in orthopedic surgery is rivaroxaban. Rivaroxaban is effective and safe in orthopedic surgery in real-world studies as in RCTs. However, in this context, data of bleeding related mortality is still scarce. Data for apixaban is currently limited.

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## **Benzodiazepine Deprescription Strategies in the Elderly Medicine In-Patient Population**

**Dr. Arian Ghassemian, Dr. Kulraj Singh, Dr. Alan Gob.**

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There is an abundance of literature outlining the potential harms of short and long-term benzodiazepine and benzodiazepine receptor agonist use in the elderly. Despite this fact, benzodiazepines continue to be prescribed even where there is poor clinical indication for their use, including insomnia and agitation. This and this is not limited to the outpatient population. As part of a quality improvement initiative targeted at benzodiazepine deprescription, we audited the three CTUs at University Hospital on five separate days and found that 25% of patients aged 65 or older had received benzodiazepines over the 5 days. We also found no strong indication for 49% of prescriptions. Insomnia, continuation of home medications, and acute anxiety/agitation were the most common cited weak indications behind these inappropriate prescriptions at our institution. We will be further exploring the root causes behind these prescriptions through interviews with the interdisciplinary healthcare team and implement strategies to curb inappropriate benzodiazepine prescription and use in the 65 and over in-patient population, tracking the effect of our interventions with regular audits of the Teams' benzodiazepine prescriptions. We hope to reduce inappropriate benzodiazepine use and prescriptions by 75% and benzodiazepine receptor agonist use by 100% by the end of fall 2018.

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## **Cost-Descriptive Analysis for Video-assisted Thoracoscopic Surgery Pleuroscopy**

**Inderdeep Dhaliwal, Dan Gillett.**

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Costs of health care are rising significantly in Canada and innovation to reduce costs while improving care is imperative. Malignant pleural effusion (MPE) affects 15,000 Canadians per year. Patients with MPE are suffering from

incurable cancer; palliative cancer patients have higher quality of life and survival when time at home is maximized. Video-assisted Thoracoscopic Surgery (VATS) Pleuroscopy and Medical Pleuroscopy (MP) are two equivalent procedures in the treatment and diagnosis of malignant pleural effusion (MPE). VATS Pleuroscopy is performed in the operating room (OR) setting; MP is performed in an endoscopy suite with same-day discharge. This study is to describe costs of VATS Pleuroscopy and MP for patients suffering from MPE, and to evaluate whether there is significant potential cost savings from MP. Ontario case costing initiative (OCCI) administrative data was used to collect cost data of VATS Pleuroscopy between March 30, 2014-April 1, 2015, this was compared to projected MP costs in an endoscopy setting. Following data collection and projections, MP is expected to save \$9574.04 per procedure; the additional costs for VATS Pleuroscopy are secondary to hospitalization and OR use. In conclusion, MP can provide a more cost efficient, effective and high quality alternative to VATS Pleuroscopy for patients suffering from MPE.

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## **The role of cyclooxygenase in colitis-associated colon cancer**

**Hayley J. Good, Elena N. Fazio, Alice E. Shin, Liyue Zhang, and Samuel Asfaha.**

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Introduction: Inflammatory bowel disease (IBD) is a major risk factor for colorectal cancer (CRC). However, the mechanism by which colitis leads to cancer is unknown. Dclk1 is a marker of colonic tuft cells. We previously showed that Dclk1+ cells are quiescent and long-lived, and remain resistant to proliferation even upon mutation of the tumour suppressor APC, but become cancer-initiating cells upon exposure to inflammation. Interestingly, Dclk1+ tuft cells express high levels of cyclooxygenase (COX)-1 and -2, the direct target of non-steroidal anti-inflammatory drugs (NSAIDs) which are known chemopreventative drugs in CRC. Thus, we aimed to determine the effects NSAIDs on colitis-associated cancer. Methods: Dclk1CreERT2/APCflox/flox mice were administered tamoxifen to induce an APC mutation in Dclk1-expressing cells. Mice

were then exposed to the colitis-inducing agent dextran sodium sulfate (DSS), followed by daily treatment with Aspirin (non-selective COX inhibitor), celecoxib, rofecoxib (COX-2 inhibitors), or vehicle. 16 weeks post-tamoxifen, colonic tumour number and size were analyzed to determine the effect of NSAIDs on tumour initiation and growth, respectively. Extent of inflammation was assessed by myeloperoxidase activity and histology, and colonic levels of inflammatory mediators were measured by qRT-PCR. Results: Treatment with Aspirin, but not COX-2-inhibitors, significantly reduced the number of Dclk1+ cell-derived colonic tumours. There was no significant difference in tumour size or degree of colitis between vehicle and NSAID-treated groups. Conclusions: These findings suggest a role for cyclooxygenase in colonic tumourigenesis arising from Dclk1+ cells. Our results suggest that Aspirin may be useful for chemoprevention of CRC in patients with IBD.

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### **Profile of Sleep Physicians in Ontario, Canada: A Secular Trend Analysis**

**Amanda Grant-Orser**, Krista Bray-Jenkyn, Britney Allen, Charles F. George, Salimah Z. Shariff, Marcus Povitz.

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Background: Sleep disorders are under-diagnosed and under-treated in Canada. Sleep medicine is a relatively new discipline entered from other primary specialties after completion of residency training. Currently, there is no traditional direct entry pathway. As a result of the increasing clinical demand for sleep physicians many specialists have added sleep medicine to their existing practice. Information on what type of physicians are practicing, how much of their practice is sleep related and if there are the estimated 1.4/100 000 required physicians needed to treat sleep apnea in Ontario is unknown. Methods: We used information from a database of continuous positive airway machine funding in Ontario from 2006 to 2013 to identify physicians practising sleep medicine and linked their information to administrative databases to characterise them by age, sex, primary specialty and practice volumes. Results: The number of sleep physicians has increased from 133 to 190 or 1.32/100 000 to 1.74/100 000 Ontario

residents over the study period. Respiriology (53-58%) remained the predominant specialty followed by psychiatry (13-16%). Sleep physicians were predominantly male, with a median age in their early 50s and an increasing proportion trained outside of Canada. Of the total volume of consultations sleep physicians saw in each year 26-32% had a diagnostic code related to sleep. Conclusions: Despite increasing numbers of physicians practicing sleep medicine, there is still a shortage of qualified physicians, either more physicians will need to be trained in this area or alternative systems of care for sleep disorders will need to be adopted.

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### **Procedure Complexity and Complications in Pulmonary Vein Ablation for Atrial Fibrillation**

**Alexander W. Grindal**, Peter Leong-Sit, Allan C. Skanes, Jaimie Manlucu, Jason Roberts, Anthony S.L. Tang, Raymond Yee, George J. Klein, Lorne J. Gula.

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Background: When medical management fails, Pulmonary Vein Ablation (PVA) can be an effective therapy to eliminate AF. The most common target for ablation is electrical isolation of the pulmonary veins. Depending on the nature of the AF, additional ablation lesion sets (eg. left atrial roof line, mitral isthmus line, fractionation ablation) may be necessary. Complications from a PVA can be serious, with a procedural risk estimated at approximately 4%. Methods: In this retrospective cohort study, we aimed to determine if ablation procedures that involve extra lesions sets in addition to pulmonary vein isolation result in increased complication rates. We examined 1,374 PVAs performed from 2009 to 2017. Of these, 984 were simple ablations (pulmonary vein isolation alone) and 390 were complex (left atrial roof line, mitral isthmus line, or fractionation ablation). Tamponade, congestive heart failure, and stroke/TIA were considered serious complications. Results: Complex procedures had a significantly greater number of ablations (31 vs 21,  $p = 0.01$ ), longer ablation duration (43 vs. 36 minutes,  $p < 0.01$ ), longer total fluoroscopy time (20 vs 19 minutes,  $p = 0.04$ ) and longer procedure time (244 vs 217 minutes,  $p < 0.01$ ) than simple ablations. Serious complication

rates were 1.93% vs 2.31% for simple and complex procedures respectively ( $p = 0.67$ ) and total complication rates were 7.22% vs 7.69% ( $p = 0.76$ ). Conclusions: Complex ablation procedures for atrial fibrillation have longer procedure, fluoroscopy and ablation times than simple ablation procedures, but do not appear to have a higher overall risk of serious complications.

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### **Identification of Functional Consequences of Polymorphisms in the Gene for Kidney Injury Molecule-1**

Ola Z. Ismail, Shivam Singh, Xiaojing Gu, Bradly Shrum, Ji Yun Lee, Xizhong Zhang and Lakshman Gunaratnam.

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During Acute kidney injury (AKI), apoptotic cells undergoing secondary necrosis and necrotic cells release their immunogenic contents into the extracellular milieu. Phagocytes ingesting these dead cells and suppress inflammation. Kidney Injury Molecule-1 (KIM-1) is a cell-surface glycoprotein upregulated on tubular epithelial cells (TECs) during AKI. We uncovered that KIM-1 protects against AKI by enabling TECs to recognize and ingest dead cells. The gene coding for KIM-1 (HAVCR1) is highly polymorphic, but the functional relevance of human KIM-1 polymorphisms in AKI have not been studied. To test the hypothesis that HAVCR1 polymorphisms in region coding for the KIM-1 extracellular domain decrease the ability of TECs expressing the variant KIM-1 proteins to phagocytose apoptotic cells in vitro. We generated the cDNA variants using site-directed mutagenesis and an expression plasmid encoding wild type KIM-1 (pcDNA3-KIM-1). We then expressed the pcDNA3 vector, vector encoding wild type, or HAVCR1 variants in HEK-293 cells using transient transfection. We generated constructs for 2 high-frequency HAVCR1 coding variants. Total protein expression in HEK-293 cells was equal between the KIM-1 variants and wild type KIM-1. However, cell surface expression was variable. Phagocytic uptake of apoptotic cells was significantly reduced in HEK-293 cells expressing the variants compared to those expressing wild type, providing strong evidence of functional compromise of the protein encoded by these

alleles. This is the first study to provide evidence that human polymorphic variants in HAVCR1 can produce functional changes in the KIM-1 protein. This work strengthens the plausibility of a biological role for KIM-1 in humans.

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### **Identifying and targeting cancer stem cells in colorectal cancer**

Amber Harnett, Alice Shin, Hayley Good, Samuel Asfaha.

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Advanced colorectal cancer (CRC) is associated with tumours that are resistant to conventional therapy. These resistant tumours are believed to arise from cells known as cancer stem cells (CSCs). However, it's not known whether more than one CSC population exists and this may influence treatment modalities. Our lab recently identified keratin-19 (K19) as a potential CSC marker. Therefore, I will determine if K19 labels a CSC population and assess the effects of ablating a known Lgr5+ CSC on intestinal tumour initiation and growth to assess which CSC is the ideal target to halt tumour growth. To determine if K19 labels a CSC population, tumour bearing K19-CreERT;TdTomato mice were administered tamoxifen to induce lineage tracing within established tumours. 8-weeks post treatment, adenomas were analyzed using fluorescence microscopy. To assess the role of Lgr5+ CSCs in tumour initiation and growth in vivo, Lgr5-DTR-eGFP mice were administered diphtheria toxin (DT) or saline throughout tumourigenesis. The groups were compared with respect to tumour burden and histology at 28 weeks of age. To determine the role of Lgr5+ CSCs in established tumours in vitro, tumour organoid size upon DT treatment was monitored. Our results indicate that K19 labels a CSC population in vivo and ablation of Lgr5+ CSCs cells has no effect on tumour initiation or growth in vivo and in vitro. These results suggest additional CSC populations exist besides Lgr5, which are important for tumour initiation and growth. Consequently, these findings have important clinical implications for the development of new therapies.

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## **Evolving Patterns of Reactive Arthritis**

**Hayes, K., Hayes, R., Pope, J.**

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548 members of the Canadian Rheumatology Association were emailed and 67 completed our survey. Questions covered: prevalence, tests, treatments and perceptions on changes in incidence, severity and causes of Reactive arthritis (ReA). Descriptive statistics were used. Results were not confirmed by chart audits. 47% of rheumatologists perceived ReA to be declining in incidence (6% perceived ReA to be increasing). 39% thought that the common causes are changing. Acute, chronic, and recurrent ReA were perceived to have similar frequencies. Asymmetric oligoarthritis occurred in the majority of ReA seen (78%). Full triad ReA was reported to occur in 21% of ReA cases, and patients with conjunctivitis were likely to exhibit the rest of the triad. Patients with recurrent ReA were more likely to exhibit the full triad (43%) compared to acute or chronic ReA (14%). Reported common causes of ReA included infectious causes (35%), mostly by 'unknown' infectious organisms, followed by gastrointestinal infections and STI's. Reported common tests ordered included testing for chlamydia (66%), CRP (62%), and HLA (50%). Imaging was ordered by 39% with sacroiliac joint imaging ordered by 21%, X-rays of the affected joints by 15%, and other imaging by 7.5%. Reported common treatments for ReA were NSAIDs (97%), intra-articular corticosteroid injections (65%), and DMARDs (45%). TNF inhibitors were used at least occasionally in chronic ReA (67%). In conclusion, ReA may be decreasing in frequency and severity (with less than full triad of symptoms and less chronic ReA). Full triad ReA was thought to be linked with recurrent ReA.

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## **Identification of a novel IHH insertion causative of brachydactyly type A1**

**Rosettia Ho, Adam D. McIntyre, Brooke A. Kennedy, and Robert A. Hegele.**

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Isolated brachydactyly is an umbrella term describing disproportionately shortened fingers and toes, often following an autosomal dominant complex malformation syndrome. To date, although various forms of brachydactyly have been characterized and 8 causative genes have been found, many subtypes remain genetically undefined. Gene discovery is the critical starting point in understanding the molecular mechanisms underlying these unexplained brachydactyly subtypes, providing robust diagnoses, and developing targeted treatments. Here, we describe a 15-year-old unsolved medical case involving an Ontario family with a history of brachydactyly, in which whole-exome sequencing and bioinformatics analysis identified a novel variant for brachydactyly type A1 (exon 1, c.285\_287dupGAA, p.Glu95\_Asn96insLys) in the Indian hedgehog (IHH) gene. This novel variant co-segregated with affected status in the pedigree and was associated with: 1) shortened middle phalange length by 21.1% ( $P < 0.001$ ); 2) shortened palm length by 13.8%, ( $P < 0.01$ ); 3) reduced digit-palm ratio by 6.8% ( $P < 0.03$ ); and 4) reduced stature by 9.5% ( $P < 0.001$ ). We report the first IHH insertion in the literature, resulting in classic BDA1. These data highlight the power of whole-exome sequencing as a tool for identifying the molecular basis of rare disorders. Furthermore, they indicate the ability of next-generation sequencing to solve or clarify the genetic basis of "cold cases". Determining the molecular basis of genetically unexplained disorders will allow for increased understanding of disease mechanisms, and will help other health care providers caring for families with the same condition caused by the same gene.

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## **Implementation of osteoporosis screening and prevention strategies for hematology patients on long-term corticosteroids**

**Melissa Holdren, Alan Gob.**

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Background: Long-term corticosteroid use is well known to cause osteoporosis. Despite this knowledge many patients on long-term corticosteroids do not have the appropriate screening, follow-up and treatment for osteoporosis. There exists a gap between

knowledge of the adverse effects of corticosteroids and clinical practice measures taken to preventing these adverse effects. It is not well known how to implement a system whereby there is appropriate identification and treatment of osteoporosis for those on long-term corticosteroids. With the vast number of conditions treated with corticosteroids across many specialities we require a way to implement the knowledge we have of the adverse effects of corticosteroids into appropriate screening and treatment tools in order to prevent further harm. Our AIM was to improve osteoporosis screening by 50% in hematology patients on long-term corticosteroids. Methods: Baseline performance data was collected with regards to osteoporosis screening and prevention performed by hematologists at London Health Science Center. Process mapping was performed at our specified clinical site. Root cause analysis and creation of a fishbone diagram was performed to identify areas to target improvement methods. Results: Data pending Conclusion: This project will look to characterize factors contributing to lack of best practices with regards to osteoporosis screening for those on long-term corticosteroids and propose interventions to improve on implementation of best practices.

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### **Use of next-generation sequencing to detect copy number variants in the routine molecular diagnosis of familial hypercholesterolemia**

**Michael A. Iacocca**, Jian Wang, Jacqueline S. Dron, Thomas Lagace, John F. Robinson, Adam D. McIntyre, Henian Cao, Ruth McPherson, Robert A. Hegele.

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Background/Aim: Familial hypercholesterolemia (FH) is the most frequent monogenic disorder encountered in clinical practice, affecting 1 in 250 individuals worldwide. Routine diagnosis of FH is trending towards use of next-generation sequencing (NGS) panels to interrogate FH-associated genes LDLR, APOB, PCSK9, LDLRAP1, APOE, and STAP1. While traditional NGS analysis has focused on detection of small-scale DNA variants, large-scale copy number variants (CNVs) have remained largely overlooked. Here, we determined the ability of

applying a bioinformatic method to NGS data for the detection of CNVs in FH-associated genes. Methods: In 612 FH patient samples we sequenced FH-associated genes using our LipidSeq NGS panel. Subsequent CNV analysis was performed using the NGS bioinformatics tool CNV Caller (VarSeq®). MLPA and array comparative genomic hybridization (aCGH) methods have been used to confirm the presence of CNVs. Results: In 612 FH patient samples, we detected 38 whole-exon CNVs in the LDLR gene, and 2 whole-gene duplications in the PCSK9 gene using our novel bioinformatics method. All called CNV events in LDLR were confirmed by MLPA, while PCSK9 events were confirmed by aCGH. Patients harbouring these CNVs present with an extreme clinical phenotype. Conclusions: Analysis of NGS data for CNV identification shows potential to become a routine diagnostic test for those with suspected FH. While this cost-effective method has demonstrated accurate CNV detection in LDLR, it also allows for novel CNV screening in additional FH-associated genes with an ability to discover new genetic mechanisms for FH; as seen with the PCSK9 whole-gene duplication event discovered here.

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### **Prophylactic RVAD for High Risk Valve Surgery**

**Atul K. Jaidka**, Sabe De, Michael W. A. Chu.

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Right ventricular failure (RVF) post cardiac surgery can be devastating for a patient as our usual treatment modalities of afterload reduction, contractility optimization, vasopressors and rescue mechanical support often are not enough. The aim of this study is to propose a novel strategy of inserting a right ventricular assist device (RVAD) prophylactically during the primary OR for those at high risk for RVF (pre-operative RV dysfunction or severe pulmonary hypertension) undergoing valvular surgery. We conducted a retrospective cohort study examining patients high risk for RVF supported with a Thoratec Centrimag inserted during primary OR for valvular surgery. From 2014 to 2017, ten patients underwent the surgery and their demographics, pre-operative hemodynamics, surgical methods, post-operative course and follow-up survival and

echocardiogram were reviewed. All ten patients had successful RVAD insertion, RVAD wean, and survived to hospital discharge. Generally, the RV showed echocardiographic evidence of worsening function post-operatively but recovery at the time of follow-up. Patients required minimal inotropic support and no other mechanical support apart from two IABPs. Major complications included 4 patients with respiratory failure, infections (2 sternal and 1 sepsis), metabolic encephalopathy and delirium, and no major bleeding. There were two late mortalities, iatrogenic early valve thrombosis and COPD exacerbation. Despite the high risk for RVF, prophylactic insertion of the RVAD was able to support RV recovery through valve surgery, resulting in 100% in-hospital survival and without a significant increase in surgical complications. This study rationalizes the usage of prophylactic RVAD and promotes the need for further prospective study.

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### **Effects of Fetal Growth Restriction on the Surfactant System in Response to Sepsis**

**Reza Khazaei**, Lynda A McCaig, Zhon Huang, Daniel B Hardy, Cory M Yamashita, Ruud AW Veldhuizen.

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**Background:** Sepsis is one of the major causes of severe lung injury. A common mechanism contributing to lung injury is alterations to surfactant, a lipid-protein mixture coats the inside of the lung and eases the lung expansion during respiration. Due to lack of effective pharmacological therapies the mortality associated with this condition is over 30%. Our research focuses on identifying risk factors that indicate a susceptibility to the disease, which could provide new and early therapeutic options. One potential risk factor is fetal growth restriction (FGR), which is defined by low birth weight. We hypothesize that FGR is a risk factor for developing lung injury through surfactant alterations. **Methods:** We employed an FGR rat model induced by maternal protein restriction. At postnatal day 130, male and female offspring received either an intraperitoneal injection of saline or fecal slurry to induce sepsis. After 6hr, arterial blood and surfactant were taken for cytokine and surfactant analysis. **Results:** FGR

was confirmed by significant decrease in birth weight as compared to controls. Septicemia was confirmed by blood culture in animals receiving the fecal slurry. Surfactant analysis showed significant reduction in the surfactant content in septic male FGRs. Non-FGR groups demonstrated no changes in surfactant content between septic and shams. **Discussion & Conclusion:** Surfactant reduction in FGR septic males supports that FGR is a risk factor for developing surfactant impairments. To further evaluate FGR as a risk factor contributing to surfactant alterations and lung injury, we will assess the surfactant biophysical properties and lung histology.

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### **Effects of differentially polarized macrophages on osteoarthritis gene expression profiles in fibroblast like synoviocytes**

**Kevin Krysiak**, Gaëlle Wambiecke, Tom Appleton.

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Osteoarthritis (OA) involves the progressive breakdown of articular cartilage and inflammation of the synovium. Macrophage-like synovial cells and fibroblast-like synoviocytes (FLS) are found within the synovium. During OA, macrophages (M $\phi$ ) are recruited from the periphery and depending on their polarization either have pro-inflammatory (M1-like) or anti-inflammatory (M2-like) effects on joint tissues through different cytokine secretion profiles and enzymes. I aim to understand the effect that differentially polarized macrophages will have on FLS. I hypothesize that M1-like M $\phi$  will increase OA-related gene expression profiles in FLS, whereas M2-like M $\phi$  will have an opposite effect. FLS and blood was isolated from healthy male Sprague-Dawley rats. Peripheral blood mononuclear cells were separated based on density, and a magnetic-activated cell sorting column was then used to enrich monocytes. FLS cells were seeded into wells and co-cultured with differentially polarized macrophages on inserts. Macrophages were kept un-polarized by using serum-free media and M-CSF (50ng/mL). M1 polarization was achieved by using serum-free media supplemented with IFN- $\gamma$  (50ng/mL) and LPS (10ng/mL), whereas M2 polarization was achieved using IL-4 (10ng/mL)

and M-CSF (50ng/mL). FLS were harvested 48 hours after co-culture and RNA was isolated. It is predicted that M1 and M2 polarization will result in qPCR data respectively showing a relative increase and decrease in OA-related gene expression, when compared to the un-polarized control. A one-way ANOVA will be used to draw these conclusions. These results will provide a deeper understanding of cell signaling that occurs in knee joint tissue, and a basis for further exploration.

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### **Seasonality of New Early Inflammatory Arthritis Cases: Preliminary Results from the Canadian Early Arthritis Cohort**

**F. Kudaeva**, M. Speechley, N. Klar, O. Schieir, S. Bartlett, C. Hitchon, G. Boire, B. Haraoui, E. Keystone, D. Tin, C. Thorne, V. Bykerk on behalf of CATCH investigators.

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**Background:** Disease clustering suggests a possible environmental cause. However, confirming the causes of time-place clustering is challenging. Rheumatoid arthritis (RA) is an autoimmune disease that may be triggered by environmental factors via molecular mimicry, epitope spreading, B-cell-mediated pathway, bystander activation and superantigens. Putative infections may also cluster. **Objectives:** To study the seasonal distribution of early inflammatory arthritis (IA) onsets in a Canadian sample, and to analyze whether it corresponds to seasonal influenza outbreaks. **Methods:** Data from an incidence cohort of adults (>18 years) with early IA from the Canadian Early Arthritis Cohort (CATCH), with recent onset confirmed RA or IA (probable RA). **Inclusion criteria:** patients enrolled in CATCH from January 2007 - January 2017, with <13 months symptom duration. Patient-reported date of symptom onset and physician-reported date of IA onset were used to estimate the monthly frequency of early inflammatory arthritis onsets. Monthly influenza case frequencies from September 2010 - December 2016 were retrieved from the Public Health Agency of Canada's FluWatch national surveillance system of confirmed influenza A and B cases. Time-series Poisson regression analyses were performed to assess the non-random covariance of IA and influenza with

different hypothesized time lags. **Results:** A total of 2262 with early IA were included. Patient-reported IA onset was more frequent in winter months compared to other seasons ( $p=0.0021$ ), with peaks in January. The ten-year aggregated data also showed January peaks of IA onset. There was a positive linear correlation between the number of IA and influenza A onset ( $r=0.23$ ,  $p=0.045$ ).

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### **A Systematic Review and Meta-Analysis of Viral Exposures as a Risk Factor for Rheumatoid Arthritis**

**F. Kudaeva**, M. Speechley, J. Pope.

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**Background:** Rheumatoid arthritis (RA) is an autoimmune disease with a complex and poorly understood etiology. Infections are viewed as triggers of some autoimmune disorders, including RA. **Objectives:** The purpose of this systematic review was to summarize the evidence relating to the association between putative viral exposures and the development of RA. **Methods:** A systematic literature search was conducted using MEDLINE-OVID, EMBASE-OVID, PUBMED and Cochrane library databases. **Results:** Of 6724 citations, 78 studies were selected for review, and 48 were included in the meta-analysis. Studies had poor quality. The odds of parvovirus B19 (PBV19) infection were increased in RA patients than in controls ( $p=0.02$ ). Patients with RA had not significant OR of anti-Epstein-Barr nuclear antigen (EBNA) ( $p = 0.75$ ), but significant OR of anti-viral capsid antigen (VCA) ( $p=0.02$ ) and anti-early antigen (EA) ( $p=0.01$ ). Cytomegalovirus (CMV) was not associated with RA ( $p=0.36$ ). Chronic hepatitis B (HBV) was not associated with RA in 5 case-control ( $p=0.22$ ) and 1 cohort studies ( $p>0.05$ ). Chronic hepatitis C (HCV) was associated with increased risk of RA in 7 case-control (OR (95% CI) = 2.82 (1.35; 5.90,  $p=0.006$ ) and 1 cohort studies (HR 2.03 (1.27, 3.22),  $p<0.01$ ). There seems to be a risk of persistent arthritis after Chikungunya fever (CHIKV) ( $p=0.002$ ). **Conclusions:** There is a risk of RA after Parvo B19 infection and possibly HCV but not EBV or HBV. CHIKV is associated with the persistent inflammatory arthritis.

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## **Synovitis in Early Post-Traumatic Knee Osteoarthritis: Effects on Healthy Chondrocytes**

**Yue Lai-Zhao**, C. Thomas G. Appleton.

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**Background:** Osteoarthritis (OA) causes low-grade synovitis. Whether synovial tissue macrophages promote or protect against early knee OA is unknown. **Objectives:** We investigate whether synovial macrophages influence OA-like changes in healthy articular chondrocytes using primary cells from a post-traumatic knee OA (PTOA) model in male Sprague-Dawley rats. Early cartilage damage develops within 4 weeks of anterior cruciate ligament transection and medial meniscus destabilization. **Methods:** Whole knees were obtained from rats with PTOA or controls (sham surgery) 4 weeks post-surgery and histologically processed for Krenn synovitis grading. Mixed synoviocytes were isolated from PTOA, sham surgery, or age-matched naïve joints, expanded in culture, and co-cultured in trans-well systems with chondrocytes from age-matched healthy knee joints for 48 hours. Chondrocyte apoptosis was measured by annexin V fluorescence assay. Proteoglycan release was measured in co-culture medium. RNA was isolated for relative quantification of gene expression by qPCR. **Results:** Histopathology confirmed low grade synovitis in PTOA knees vs. controls. Gene expression testing is under way; expected OA-like changes in chondrocytes co-cultured with PTOA synovium include increased apoptosis, up-regulated matrix metalloprotease (Mmp13, Adamts5) and cytokine (Tnfa, Ccl2) genes, decreased matrix (Col2a1, Acan) and transcription factor (Sox9) expression, and lower proteoglycan release. **Significance:** These results validate our co-culture paradigm and will allow us to test whether PTOA synovium-induced changes are dependent on macrophage polarization state. Using a similar co-culture paradigm, we will manipulate PTOA synovial macrophages through depletion, M1, or M2 polarization to determine if macrophages are candidates for therapeutic translational studies in vivo.

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## **Cardiac Function in Sepsis: A Systematic Review of the Effects of Sepsis on Cardiac Function**

**Spencer D Lalonde**, Marat Slessarev MD, Fran Priestard MSc, Ian Ball MD.

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**AbstractObjective:** To review the evidence regarding the effects of sepsis on cardiac function measured non-invasively as systolic function through echocardiography or multi-gated acquisition (MUGA) scans. **Background:** Sepsis is a common clinical presentation, and involves a systemic inflammatory response to a source of infection. Cardiac dysfunction in the context of sepsis can have clinically relevant outcomes including mortality and overall morbidity. There are mixed reports on how the heart responds to sepsis despite routine use of non-invasive measures of cardiac systolic function and its guidance in risk stratification and medical therapy. Furthermore, the overall course of cardiac dysfunction and potential recovery in sepsis has not been fully explored. **Methods:** A systematic review was conducted to evaluate the evidence of the effects of sepsis on cardiac function measured by non-invasive tests including echocardiography and MUGA scans. The search strategy included PubMed and Ovid MEDLINE up until April 10th 2017 and key words included sepsis, ejection fraction, LVEF, RVEF, echocardiography, heart function ventricular dysfunction and cardiac output. The study was registered on PROSPERO and articles were uploaded and selected on COVIDENCE. A total of 1707 articles were selected for screening of which 62 were selected for inclusion. A narrative synthesis was conducted using aggregate data from the included studies and where common metrics were reported forest plots were prepared. Funnel plots were used to assess publication bias. **Results:** Pending analysis **Conclusions:** Pending analysis

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## **Survival and Safety Outcomes of Intensive Care Unit Patients Discharged Directly Home – A Direct from ICU Sent Home Study**

**Vincent Issac Lau**, Fran Priestap, Joyce Lam, John Basmaji, Ian Ball.

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**Objectives:** Evaluate outcomes (mortality, morbidity, unplanned return visits) of patients who are discharged directly to home (DDH) from the intensive care unit (ICU). **Subjects/Intervention:** All adult patients who were either discharged directly home (DDH Recruited and Non-Recruited cohorts) from ICU, or discharged home within 24 hours after ward transfer (Ward Transfer cohort). **Results:** All three patient cohorts had 0% mortality at 8 weeks post-discharge. The unplanned return visit (URV) rate for the Recruited cohort was 24% (ER 18%, Ward 4%, ICU 1%), while the rate for the Non-Recruited cohort was 52% (ER 34%, Ward 14%, ICU 3%) and the Ward Transfer cohort was 46% (ER 17%, Ward 26%, ICU 3%) ( $p = 0.005$ ). No home support was available for 7% of the DDH Recruited cohort. 24% of patients had funded home care nursing, but the majority (81%) of patients relied on help from friends/family. **Conclusions:** Recruited DDH patients experienced very good 8 week post-discharge outcomes with 0% mortality, and a low rate of ICU readmission (1%) or ward readmission (4%), but not an insignificant rate of ER visits (18%). Recruited DDH patients had better outcomes compared to non-recruited DDH patients and patients transferred briefly to the ward prior to discharge home.

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## **Kidney Injury Molecule-1 Mitigates Tissue Damage from Transplant Renal Ischemia Reperfusion Injury**

**Ji Yun Lee**, Ola Ismail, Xizhong Zhang, Aaron Haig, Dameng Lian, Lakshman Gunaratnam.

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Ischemia-reperfusion injury (IRI) during kidney transplantation predisposes to delayed graft function, rejection, and premature graft failure. Exacerbation of tissue damage and alloimmune

responses may be explained by necroinflammation: an autoamplification loop of cell death and inflammation, which is mediated by the release of danger-associated molecular patterns (e.g. HMGB1) from uncleared apoptotic and necrotic cells that activate both innate and adaptive immune signaling pathways. Kidney Injury Molecule-1 (KIM-1) is a phosphatidylserine receptor that is upregulated on injured tubular epithelial cells and enables them to clear apoptotic and necrotic cells during acute injury. Our objective was to determine if KIM-1 in the donor kidney protects from transplant IRI and graft dysfunction by clearing dying cells. We performed syngeneic kidney transplants using KIM-1<sup>+/+</sup> or KIM-1<sup>-/-</sup> mice as donors and KIM-1<sup>+/+</sup> mice as recipients. We evaluated renal function, survival, tissue injury, tubular obstruction, cell death, infiltration of immune cells, expression of pro-inflammatory cytokines, HMGB1 release and Kim-1 expression at 3-7 days post-transplant. We found persistent KIM-1 expression in KIM-1<sup>+/+</sup> kidney grafts post-transplantation. Compared to KIM-1<sup>+/+</sup> kidney recipients, KIM-1<sup>-/-</sup> kidney recipients exhibited significantly more renal dysfunction, cell death, tubular obstruction, and graft failure. KIM-1<sup>-/-</sup> grafts also had more inflammatory cytokines, infiltrating neutrophils and macrophages compared to KIM-1<sup>+/+</sup> grafts. Most significantly, passive release of HMGB1 from uncleared apoptotic and necrotic cells led to higher serum HMGB1 levels and increased proinflammatory macrophages in KIM-1<sup>-/-</sup> kidney recipients. Our data identify an endogenous protective mechanism against necroinflammation in kidney grafts that may be of therapeutic relevance in transplantation.

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## **Hemodynamic Response to Non-Pneumatic Compression Stockings in Patients with Kidney Diseases**

**Jack Li**, Ryan Marinovich, Tanya Tamasi, Kathleen Quinn, Lisa Crowley, Steven Wong, & Christopher McIntyre.

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**BACKGROUND:** Intradialytic hypotension is a common complication of hemodialysis, and repeated events may lead to hemodynamic stress, and results in ischemic injuries such as

myocardial stunning. Administration of anti-shock non-pneumatic compression stockings to the lower body and limbs has demonstrated hemodynamically stabilizing effects in other settings, and may provide similar benefits in the hemodialysis population. However, further characterization of this intervention is needed prior to large scale trial. Therefore, we conducted this pilot study to assess the effect of compression stockings on patients with kidney disease, and to characterize the hemodynamic response at rest. METHODS:Fifteen individuals were enrolled in the study (five each, from healthy, stage 4-5 non-dialysis, and hemodialysis cohorts). Hemodynamic parameters such as cardiac output, peripheral vascular resistance, and blood pressure were measured. Changes in left ventricular ejection fraction and strain were separately measured assessed. Measurements were done before and after the application of compression stockings.RESULTS:All enrolled individuals tolerated the application of compression stockings without complications. Application of compression stockings resulted in an average of 1.8% increase in cardiac output, compared to 0.6% in healthy patients, and -4.7% in non-dialysis CKD patients. However, inconsistent responses were observed within each group.CONCLUSIONS:Application of compression stockings to CKD and dialysis patient was well-tolerated, however, in this small-scale study, no consistent hemodynamic changes were observed. Therefore, before large scale trial is undertaken to assess the benefit of compression stockings during dialysis, further studies are needed to better characterize clinical features that may predict better responses.

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### **Utilization of Inpatient Checklists for Junior Residents in the Clinical Teaching Unit**

Jack Li, Alan Gob.

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BACKGROUNDThe Internal Medicine service is a complex environment with a high volume of patients. In addition to medical training, junior members of the team play an important role maintaining daily clinical workflows. The efficiency of these teams directly impacts patient turnover, which has direct effect on bed

availability and Emergency Department wait times. Focusing on timely patient discharge, previous investigations have identified key preventable causes for discharge delays. Focusing on these causes, a series of checklists were developed to aid daily rounding and discharge planning. The goal of this study is to assess the impact of these checklists on trainee experience and patient care. METHODThree CTU teams at University Hospital were involved in the study over a three-week period. One team had checklists introduced on Week 2, the other teams had checklist introduced on Week 3. Admission documentation, medication reconciliation before discharge, and list utilization were measured. RESULTSIn the team with the highest checklist utilization (77%), admission medication reconciliation and resuscitation status complete rate increased by 18%; early discharge medication reconciliation in anticipated discharges increased by 35%. The percentage of patients discharged before 11 am increased by 15%. Teams with lower checklist utilization rates did not show similar improvement. A survey study showed favourable reception to the use of the checklists. CONCLUSIONSUtilization of inpatient care checklists provides educational benefits for trainees and may improve patient care and flow within the hospital system. Further trainee education may be needed to ensure adequate implementation of checklists.

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### **Quality Improvement Study to Assess the Safety of Transition and Hemoglobin Stability from Erythropoietin to Darbepoetin**

Lotfy K, Sadagah L.FHouse AA.

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Background: Erythropoietin (EPO) is an effective treatment for renal anemia. Medication errors are common, often occurring as errors of omission. Darbepoetin is a single weekly dose potentially reducing risk of error and nursing workload. Objective: Quality improvement study assessing the safety of transition to darbepoetin and hemoglobin stability.Methods: Hemodialysis patients for a minimum of 6 months, on EPO a minimum of 3 months with no dose change,transfusion, chemotherapy, hospitalization or major surgery. Darbepoetin

conversion using a customized nomogram. Patient characteristics obtained 3 months prior and following conversion. Results: 201 patients. Mean age was 66 years, weight 78.5 kg, 44.3% female, on dialysis 1438 days. Mean EPO dose was 9072 units/week, and darbepoetin dose at conversion was 29.4 mcg/week, unchanged 3 months later, at 29.7 mcg/week. Mean ratio of EPO to darbepoetin conversion was 299.8:1. At 3 months 78% of patients had no change in darbepoetin dosing, 11% decreased >10 mcg and 11% increased >10 mcg. There were no laboratory or clinical characteristics to predict increase or decrease in dose. Mean hemoglobin prior to conversion (109.9 g/L) did not differ from 3 month post conversion (108.6 g/L) (P=0.18). Mean transferrin saturation increased from 26.6% to 29.6% (P= 0.001), while ferritin did not change. Conclusion: patients were safely converted to once weekly darbepoetin at a mean ratio of nearly 300:1 while maintaining stable hemoglobin. The nomogram was successful in 78% of cases. This offered less frequent doses, decreased nursing workload and cost while potentially reducing medication error.

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### **Isolated Secondary Adrenal Insufficiency in the Absence of Hypophysitis Secondary to Immune Checkpoint Inhibitors**

**Mary Lu MD**, Christopher D'Sylva MD FRCPC, Irene Hramiak MD FRCPC, Tisha Joy MD FRCPC FACE.

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**BACKGROUND:** Use of immune checkpoint inhibitors (ICPIs) for treating advanced malignancies has uncovered various endocrinopathies, often as immune-related adverse events (irAEs). **CASE:** A 72-year-old man with metastatic melanoma presented with a 1-week history of fatigue, dizziness, nausea and vomiting. He received ipilimumab with nivolumab for 2 months, then nivolumab alone for the past 4 months. On presentation, blood pressure was 94/67 mmHg; serum sodium was 124 mmol/L. Secondary adrenal insufficiency was suspected and managed empirically with dexamethasone, after random serum cortisol and ACTH levels were drawn. Serum cortisol returned at 30 nmol/L (reference range: 82-413 nmol/L) with

undetectable ACTH level, consistent with the diagnosis. No other pituitary hormonal insufficiencies were present. Magnetic resonance imaging revealed stable brain metastases, no hypophysitis and normal-sized pituitary fossa. He was discharged on prednisone 7.5 mg daily and subsequently transitioned to hydrocortisone 20 mg daily. During 9 months of follow-up, no recovery of the pituitary-adrenal axis and no further pituitary hormonal insufficiencies have occurred. **DISCUSSION:** Nivolumab and ipilimumab are ICPIs, augmenting T-cell function against tumour cells, and potentially against non-cancerous cells, the latter leading to irAEs, including various endocrinopathies. To date, there are 12 case reports of secondary adrenal insufficiency without documented evidence of hypophysitis, as in our case. irAEs can occur even months following discontinuation with poor prognosis for recovery in cases of adrenal insufficiency. Our case demonstrates that although symptoms of nausea, vomiting, and fatigue are common among oncology patients, clinical suspicion for adrenal insufficiency should remain high among patients receiving ICPIs.

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### **Prevalence, Risk Factors, and Costs of Aminosaliclylate Use in Crohn's Disease: A Systematic Review and Meta-analysis of Clinical Trials**

**Christopher Ma**, Susan J. Dutton, Lauren E. Cipriano, Siddharth Singh, Claire E. Parker, Tran M. Nguyen, Leonardo Guizzetti, Jamie Gregor, Nilesh Chande, Pieter Hindryckx, Brian G. Feagan, and Vipul Jairath.

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**Background:** Aminosaliclylates are the most frequently prescribed drugs for patients with Crohn's disease (CD), yet evidence to support their efficacy as induction or maintenance therapy is controversial. **Aims:** To quantify aminosaliclylate use in CD clinical trials, identify factors associated with use, and estimate aminosaliclylate treatment costs. **Methods:** MEDLINE, Embase, and CENTRAL were searched to April 2017 for placebo-controlled trials in adults with CD treated with corticosteroids, immunosuppressants, or biologics. The proportion of patients co-

prescribed aminosalicylates at trial entry was pooled using a random effects model. Multivariable meta-regression was used to identify factors associated with aminosalicylate use. Treatment costs were estimated using the Ontario Drug Benefit Program. Results: Forty-two induction and ten maintenance trials were included. The pooled proportion of patients co-prescribed aminosalicylates was 45% [95% CI: 40%-51%] in induction trials and 49% [95% CI: 35%-64%] in maintenance trials. Aminosalicylate use was less common in studies published after 2005 (OR 0.47 [95% CI: 0.32-0.71],  $p < 0.001$ ) and in trials enrolling patients with moderate-to-severe disease (OR 0.38 [95% CI: 0.22-0.66],  $p < 0.001$ ). Whilst a decline has been seen over time, 35% of CD patients were still using aminosalicylates in contemporary trials from the last five years. The estimated annual cost for the lowest price mesalamine formulation is approximately \$32 million for the CD population in Canada. Conclusions: Over one-third of CD patients entering clinical trials are co-prescribed oral aminosalicylates. A definitive trial is needed to inform the conventional practice of using aminosalicylates as maintenance therapy in CD.

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### **Systematic Review and Meta-Analysis: Endoscopic and Histologic Placebo Rates in Induction and Maintenance Trials of Ulcerative Colitis**

**Christopher Ma**, Leonardo Guizzetti, Remo Panaccione, Richard N. Fedorak, Rish K. Pai, Claire E. Parker, Tran M. Nguyen, Reena Khanna, Niels Vande Casteele, Geert D'Haens, William J. Sandborn, Brian G. Feagan, and Vipul Jairath.

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**Background:** Regulatory requirements for claims of mucosal healing in ulcerative colitis (UC) will require demonstration of both endoscopic and histologic healing. Quantifying these rates is essential for future drug development. **Aims:** To meta-analyze endoscopic and histologic placebo response and remission rates in UC randomized controlled trials (RCTs) and identify factors influencing these rates. **Methods:** MEDLINE, EMBASE, and the Cochrane Library were searched from inception to March 2017 for placebo controlled trials of pharmacological

interventions for UC. Endoscopic and histologic placebo rates were pooled by random effects. Mixed effects univariable and multivariable meta-regression was used to evaluate the influence of patient, intervention, and trial-related study level covariates on these rates. Results: 56 induction (placebo  $n=4,171$ ) and eight maintenance trials (placebo  $n=1,011$ ) were included. Pooled placebo endoscopic remission and response rates for induction trials were 23% [95% confidence interval (CI): 19-28%] and 35% [95% CI: 27-42%] respectively, and 20% [95% CI: 16-24%] for maintenance of remission. The pooled histologic placebo remission rate was 14% [95% CI: 8-22%] for induction trials. High heterogeneity was observed for all outcomes (I<sup>2</sup> 56.2%-88.3%). On multivariable meta-regression, the only covariate independently associated with significantly lower endoscopic placebo remission rates was central endoscopy reading (16% vs. 25%; OR=0.52, [95% CI: 0.29-0.92],  $p=0.03$ ). Conclusions: Placebo endoscopic and histologic rates range from 14-35% in UC RCTs but are highly heterogeneous. Standardization of outcome definitions may reduce heterogeneity and are needed in this field.

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### **The effect of MATE1 polymorphisms on cisplatin efficacy in the treatment of head and neck cancer.**

**Mary Mahler**, Wendy Teft, Daniel Breadner, Nedal Bukhari, Sara Kuruvilla, Anthony Nichols, David Palma, Richard Kim, Eric Winquist.

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**Objectives:** Homozygosity for a single nucleotide polymorphism in the gene encoding the drug transporter Multidrug And Toxin Extrusion protein 1 (MATE1) is associated with reduced ototoxicity risk from cisplatin (Winquist et al ESMO 2016). This study aims to examine if MATE1 influences the treatment efficacy of cisplatin in patients with head and neck squamous cell carcinoma (HNSCC). **Methods:** Patients were identified from a prospective, single-centre, observational cohort study of 200 HNSCC patients treated with curative intent cisplatin. Patients with HPV-related oropharyngeal and primary unknown cancers were excluded. Germline allelic variants of MATE1 were identified using TaqMan allelic discrimination assays. The disease specific

survival and overall survival of patients with MATE1 homozygous A/A variant were compared to those wild type (G/G) and heterozygous (G/A) using the log-rank test. Results 109 non-HPV-related HNSCC patients were included in the analysis. Median follow up was 33 months. 28 (25.7%) patients had disease progression or recurrence and 30 (27.5%) died. 16 (14.7%) patients expressed the MATE1 A/A variant. Median disease specific survival was 46.2 months in the MATE1 A/A patients and not reached in the G/G and G/A patients (HR 0.66 [95% CI, 0.23 to 1.82]; p=0.42). Median overall survival was 55.27 months in the MATE1 A/A patients but not reached by G/G and G/A patients (HR 1.22 [95% CI, 0.46 to 3.27]; p=0.17). Conclusion Presence of the MATE1 A/A did not compromise treatment efficacy in HNSCC patients receiving cisplatin. A small sample size and short duration of follow-up are limitations of our data.

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### **Cisplatin-induced ototoxicity in head and neck squamous cell carcinoma (HNSCC) patients treated with chemoradiation: The role of WFS1 and ABCC2 heritable variants**

**Mary Mahler**, Yiwen Zhang, Katrina Hueniken, M. Catherine Brown, Zhuo Chen, Maryam Mirshams, Jennifer Wang, Lillian Siu, Anna Spreafico, Daniel Breadner, Wendy Teft, Richard Kim, Eric Winquist, Carolyn Falls, Fei-Fei Liu, David Goldstein, Scott Bratman, Wei Xu, Andrew Hope, Geoffrey Liu.

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Background Ototoxicity is a common adverse drug reaction associated with cisplatin therapy. We evaluated the differential effect on hearing impairment in HNSCC patients by candidate polymorphisms of genes associated with either hearing loss or cisplatin function. Methods In this observational study of HNSCC patients treated with cisplatin chemoradiation, hearing impairment attributed to treatment was defined as  $\geq$  grade 2 audiometric change from (CTCAE v4.02). Patients were genotyped for 30 polymorphisms using Sequenom testing. Logistic regression evaluated associations between genetic variants and ototoxicity. Cox regression

assessed relationships between genetic variants and clinical outcomes. Results Of 246 patients who had audiometric testing pre- and post-chemoradiation, 79% were male; 76%, oropharyngeal cancers; 11%, oral cavity cancers; 8%, laryngeal cancer; 91%, stage IV; 58% had hearing loss. Two polymorphisms had significant associations with hearing loss post treatment: WFS1 rs62283056 and ABCC2 rs3740066. In an additive inheritance model, individuals with WFS1 variants had a significantly decreased risk of ototoxicity (P = 0.012; adjusted odds ratio (aOR) = 0.56; 95% CI, 0.4-0.9, per increase in one minor allele), while the minor allele of ABCC2 was associated with greater risk of ototoxicity (P = 0.016; aOR = 1.68; 95% CI, 1.1-2.6). The same genetic variants were not associated with adverse clinical outcomes in a larger cohort of 642 patients. Conclusions WFS1 genetic variant is associated with differential hearing loss in LA-HNSCC patients. An ABCC2 variant, involved with removal of cisplatin from cells, is associated with increased cisplatin-induced ototoxicity. The same genetic variants were not associated with any efficacy outcomes.

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### **Anemia in Post Kidney Transplantation Population**

**Shawna Mann**, Alan Gob.

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Post kidney transplantation anemia is common. The most common cause of post kidney transplant anemia is iron deficiency. Both anemia and iron deficiency have negative consequences for the patient. Anemia is associated with increased renal allograft failure and increased mortality. Iron deficiency is associated with heart failure and increased mortality. It is well documented that investigation for causes of anemia in the post transplant setting is under utilized. Therefore, this paper looks at current prevalence of anemia and iron deficiency in the London Health Sciences Centre kidney transplant program, current investigation rates for iron deficiency, and aims to improve these through a quality-based approach.

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## **Managing Post Kidney Transplant Care in Ontario at Home**

**Shawna Mann**, Kyla Naylor, Eric McArthur, Megan McCallum, Stephanie Dixon, Amit Garg.

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Compared to dialysis, kidney transplantation improves patient survival and quality of life, and reduces healthcare costs in the long term. Despite having an improved quality of life, patients who receive a renal transplant and live remotely, are obligated to travel long distances for follow-up visits, and this may impact the extent to which their quality of life has been improved by transplantation, as travel begets financial and time burdens. In keeping with Ontario's Patients First mandate care plans around the province are changing to reflect what patients need and want from healthcare. Renal transplantation is no exception to this. Therefore, a strategy to support more patient-centered post-transplant care in the home community has been suggested. However, there are many knowledge gaps to inform this provincial strategy. This paper aims to better inform any future strategies the province wishes to undertake in order to improve post kidney transplant care. Using data from the Institute of Clinical and Evaluative Sciences, this paper outlines the current number of kidney transplant patients in Ontario, the frequency with which they visit nephrologists and non-nephrologists, the total number of post-transplant visits by patients on an annual basis, geographically where these visits occurred and the distance patients must travel for these visits, the costs associated, and future projections of visit frequency and human resources that will be needed by the year 2027. It is hoped that this key data will be used to strengthen knowledge and develop a sound kidney transplant follow-up strategy in the future.

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**S. aureus poses a significant health concern in PWID population in Southwestern Ontario due to the bacteria's ability to survive longer in controlled-release opioid hydromorph contin.**

**Iswarya Manoharan**, Dr. Michael Silverman, Dr. Katherine Kasper, Stephannie Glockler-Lauf (preliminary).

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Introduction: Staphylococcus aureus (S. aureus) is the most common pathogen associated with injection drug use associated endocarditis (IDUaIE). Our centre has a high incidence of IDUaIE where the drug of choice is Hydromorphone controlled release (HCR). Objective: To use the injection drug preparation equipment (IDPE) of persons who inject drugs (PWID) to assess bacterial burden and survival on IDPE with HCR compared to other drugs. Methods: IDPE was collected from active PWID and plated. After a 24 hr incubation period, the bacteria were enumerated and speciation was recorded. Clinically relevant isolates of bacteria from local PWID were used to test the survival of S. aureus and S. pyogenes on drug equipment in HCR. These solutions were then heated and the remaining viable bacteria were enumerated. Results: 134 IDPE samples were collected between March 2017 and February 2018. S. aureus was detected from 3 of 11 (27%) samples of Hydromorphone immediate release (HIR), 12 of 45 (27%) samples of Meth, and 24 of 57 (42%) samples of HCR. HCR was associated with greater survival of MSSA and MRSA in solutions of the drug when compared to sterile water vehicle control. There was a 2-log reduction in the number of viable bacterial when solutions of HCR spiked with MRSA were heated. Conclusion: IPDE used to prepare HCR is more frequently contaminated with S. aureus and in vitro survival conditions showed that HCR, but not HIR, prolongs the survival of MRSA and MSSA. Heating IDPE may be an effective harm reduction strategy.

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## **Predicting the Need for Medical Rescue in Patient Admitted with Acute Severe Ulcerative Colitis**

Bashaar Al Ibrahim, **Bharat Markandey**, Vipul Jairath, Brian Yan.

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Background: High dose corticosteroids are the mainstay of treatment for hospitalized patients with acute severe ulcerative colitis (ASUC), and up to 40% of these cases require further salvage biological therapy or colectomy. Aims: To identify clinical features at the time of admission which predict the need for rescue therapy and to assess compliance with quality of in-patient care metrics. Methods: Retrospective review of adult patients with UC admitted to LHSC between January 1, 2010 and June 30, 2016. Baseline predictors of rescue therapy assessed were: Seo Index, Truelove and Witts Severity Index, WBC, CRP, Pulse, Temperature, number of bloody BM's, and Mayo endoscopic score. Care quality metrics assessed included: use of thromboprophylaxis, stool/C.diff cultures, AXR, sigmoidoscopy within 48 hours and surgical discussion. Results: 389 adult patients were identified and 135 met inclusion criteria (52.2% male; mean age 44.3 years). The majority had pancolitis (63.4%) and were receiving oral steroids (45.9%) and 5-ASAs (64.4%) on admission. With just 20% receiving immunosuppressives and 14.2% receiving anti-TNFs. The mean CRP (82), pulse (94.9) and number of bloody bowel movements (11.9) was consistent with ASUC. 36.3% received salvage infliximab. The only predictor for salvage therapy was the Mayo endoscopic score ( $p < .001$ ). Thromboprophylaxis use improved from 23% (2010) to 100% (2016). 71% had sigmoidoscopy within 48-hours and 84% had stool/C.diff cultures. Conclusions: The Mayo Endoscopic score was the only predictor of need for inpatient infliximab salvage therapy. There is room for improvement in the quality of care for inpatients with ASUC.

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## **A case of severe acute respiratory distress syndrome secondary to Legionella pneumonia treated with independent lung ventilation**

**Michael Mikhaeil**, Hailey Hobbs.

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A 41 year-old woman was intubated and mechanically ventilated in a tertiary care hospital intensive care unit for hypoxemic respiratory failure from pneumonia. Four days post-admission (PAD 4), she was diagnosed with acute respiratory distress syndrome (ARDS). She did not tolerate prone ventilation and neuromuscular blockade with lung protective ventilation led to a refractory acidosis. She was placed on Veno-venous extracorporeal membrane oxygenation (V-V-ECMO) on PAD 5. Respiratory cultures confirmed the diagnosis of Legionella pneumonia on PAD 6, and antimicrobial therapy was adjusted accordingly. The decision to pursue independent lung ventilation (ILV) was made on PAD 10 due to minimal improvement in oxygenation, in the setting of asymmetric chest x-ray infiltrate. The right lung was ventilated with high positive end expiratory pressure (PEEP) by applying a Bi-Level mode. Pressure control ventilation to target volumes of 2-3mL/kg ideal body weight was used on the left. After 48 hours of ILV, the appearance of the right lung had dramatically improved. On PAD 12, the patient was switched back to conventional ventilation, PAD 13 she was decannulated from V-V-ECMO, and PAD 16 she was successfully extubated. There is a paucity of evidence to guide ventilation in patients while on V-V-ECMO. ILV has proven effective in the presence of unilateral lung disease with different lung compliances, yet it is seldom used in intensive care units. This case illustrates the potential for ILV as a therapeutic option, when there is a unilateral disease process and conventional ventilator strategies have been exhausted.

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## **Acute Respiratory Distress Syndrome Diagnosis and Management: Assessment of Current Practice in a Tertiary Care Center Intensive Care Unit**

**Michael Mikhaeil**, Fran Priestap, Karen J. Bosma.

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Rationale: Acute respiratory distress syndrome (ARDS) is frequently unrecognized and underdiagnosed, especially in its mild forms, resulting in suboptimal management. Objective: At a tertiary care medical-surgical intensive care unit (MSICU), we sought to assess how well ARDS was being diagnosed, based on the Berlin definition and whether an evidence-based algorithm for the management of ARDS, introduced in the MSICU in 2015, was being followed. Methods: Over a 30-day period in the ICU, we assessed all admitted patients daily for the Berlin criteria for the diagnosis of ARDS. Paper and electronic charts of those fulfilling criteria were audited for the label of the ARDS diagnosis. Management was assessed daily for variables including how frequently arterial blood gas measurements were sent, whether a lung protective ventilation strategy was ordered, whether targets for tidal volume and positive end-expiratory pressure were met, the level of sedation of patients, appropriate use of neuromuscular blockade, and whether the appropriate patients were selected for prone positioning. Other variables such as fluid balance, de-escalation of the ventilation strategy, and whether the spontaneous breathing trial protocol was followed, were also assessed. Results: The 30 day audit period is currently underway. To date, 84 patients have been screened and 13 have met Berlin criteria for ARDS, and 98 patient-days of ARDS management have been assessed. The results are currently actively being collected and pending. Results from this medical audit of clinical practice will be used to guide future quality improvement initiatives in the diagnosis and management of ARDS.

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## **The Prevalence of Inappropriate Inpatient Fecal Occult Blood Testing in a Large Tertiary Healthcare Setting**

**Ahmed T. Moustafa MD MPH**, Ian Chin Yee MD, Ziad Solh MD MSc, Mayur Brahmania MD MPH.

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Background. Fecal Occult Blood testing is a recommended strategy for colorectal cancer screening in the outpatient setting. However, FOBT is often used for indications other than CRC screening in the inpatient setting. We investigated the burden of the problem. Methods. Retrospective study investigating the use of FOBT in patients presenting to London Health Sciences Centre from January 1st, 2014 to December 31st, 2016. Data was captured from a laboratory database identifying patients admitted to hospital and underwent FOBT. Results. A total of 1171 unique hospitalizations were recorded with 1 or more FOBT (s) being performed. 615 (53%) were males, and median age was 68 (IQR 0-104). FOBT was used in 179 (15%) patients between ages 0-49 and 496 (42%) above the age of 75. There was 468 (40%) positive and 703 (60%) negative FOBT's. Only 244 (20.9%) of all FOBT (s) were performed correctly with 691 tests being performed once, 186 performed twice and 50 performed greater than three times. The specialty with the highest use of FOBT included: 320 (27%) Internal Medicine, 83 (7%) Cardiovascular surgery and 82 (7%) Orthopedic surgery. The least ordering specialties included Plastic surgery, Otolaryngology, Pediatric Emergency and Pediatric surgery, with rate of 4 (0.3%), 3 (0.3%), 2 (0.2%) and 2 (0.2%), respectively. Conclusion. There were an inappropriately high number of FOBT's being performed and the problem is magnified as 79% of FOBT are performed incorrectly. We have identified system gaps where quality improvement measures can be implemented to reduce inappropriate FOBT.

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## **Intra-abdominal Hypertension Is More Common Than Previously Thought: A Prospective Study In A Mixed Medical-surgical Intensive Care Unit**

**Patrick Murphy**, Neil G. Parry, Nathalie Sela, Ken Leslie, Kelly Vogt, Ian Ball.

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**Background:** Intra-abdominal hypertension (IAH) is an under recognized phenomenon in critically ill patients. The true incidence has not been adequately determined by well powered, prospective studies which adhere to modern consensus definitions. **Methods:** Prospective observational study of consecutive ICU patients admitted to a mixed medical-surgical ICU. Intra-abdominal pressures were measured twice daily and continued until discharge or death. IAH was defined as a sustained intra-abdominal pressure > 12 mmHg. Multivariable analysis was used to identify risk factors associated with IAH and ICU mortality. **Results:** 285 patients met our inclusion criteria. Thirty percent of patients had IAH on admission and a further 15% developed IAH during their ICU stay, the majority (90%) within the first five days. The incidence of abdominal compartment syndrome was 3.0%. Obesity, sepsis, mechanical ventilation and 24-hour fluid balance (>3 L) were all independent predictors for IAH. IAH occurred in 28% of non-ventilated patients. Admission type (medical, surgical, trauma) was not a significant predictor of IAH. ICU mortality was significantly higher for patients with IAH (30%) compared to patients without IAH (11%). IAH of any grade was an independent predictor of mortality (OR 3.33, 95% CI 1.46-7.57). **Conclusions:** IAH is common in both medical and surgical patients in the intensive care setting and was found to be independently associated with mortality. Intra-abdominal pressure monitoring is inexpensive, provides valuable clinical information, and should be routinely performed in the ICU for the first 5 days of admission. Future work should evaluate the impact of early intervention/prevention of IAH.

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## **Plasma Trimethylamine-N-Oxide (Tmao) Levels may Detect Disease-Dependent Alterations in Gut Microbiota in IBD: A Pilot Study**

**Seana M. L. Nelson**, Crystal Schmerk, Yin-Yin Liao, Vipul Jairath, Keith McIntosh, Wendy A. Teft, Richard B. Kim, Aze Wilson.

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**BACKGROUND:** Ulcerative colitis (UC) is chronic, relapsing-remitting disease affecting the rectum to proximal colon. UC activity is linked to reduced gut microbial diversity. Trimethylamine-N-oxide (TMAO) is a plasma metabolite produced from dietary choline and carnitine through a microbial-mammalian pathway. Decreased plasma TMAO is associated with UC. **AIM:** Evaluate the gut microbial profile of subjects with UC and healthy controls to associate it with plasma TMAO concentrations. **METHODS:** Thirty-three subjects (13 control (C), 20 UC) were recruited and informed consent was obtained. Plasma samples were collected to measure TMAO and dietary choline concentrations. Sigmoid colon (n=132) pinch biopsies were taken to quantify the mucosal-adherent microbial profile (Bacteroides prevotella (Bp), Clostridium XIV (CXIV), Bifidobacterium longum (BI), Lactobacillus (L), Enterobacteriaceae (E)) by real-time PCR. **RESULTS:** TMAO plasma concentrations were reduced in UC compared to healthy controls (UC: 1.027±0.896, C: 5.478±3.655, p <0.001) and when adjusted for dietary choline plasma concentrations (UC: 0.149±0.232, C: 0.643±0.388, p<0.0001). Relative to the total microbiome, Enterobacteriaceae, Lactobacillus and Clostridium XIV were decreased in the UC population compared to the control population (E: UC: 0.714±1.67, C: 1.16±2.49, p=0.28; L: UC: 0.035±0.043, C: 0.042±0.057, p=0.72; CXIV, UC: 1.16±1.51, C: 2.82±5.09, p=0.28). In the UC population, Bacteroides prevotella and Bifidobacterium longum were increased relative to the total microbiome (Bp: UC: 6.37±7.22, C: 3.59±2.53, p=0.15; BI: UC: 0.32±0.51, C: 0.11±0.15, p=0.11). **CONCLUSIONS:** TMAO-producing microbiota were under-represented compared to the total microbiome in individuals with UC.

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## Changes in Skin Scores Predict Internal Organ Involvement in Early Diffuse Systemic Sclerosis

Tatiana Nevskaya, Murray Baron, Carl Baxter, Dena Ramey, Janet E. Pope.

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To estimate whether severity and changes of skin thickening over 12-months in incident diffuse cutaneous systemic sclerosis (dcSSc) are related to progression of visceral disease. Methods: dcSSc patients from the CSRG database who had disease duration  $\leq 5$  years with no evidence of end-stage internal organ damage and/or significant comorbidity at initial visit with 1 year follow-up (FU) data were included. Internal organ involvement was based on Medsger severity scores and CSRG definitions. Adjusted univariate and multivariable regression analyses were used to study the association between skin thickening and subsequent organ damage. Results: Higher baseline mRSS was significantly associated with worse disease severity (Medsger's total severity score, physician and patient global assessments), HAQ-DI and worse quality of life at baseline and 1-year FU. Baseline mRSS was not predictive of progression of organ involvement over one year. Improvement in mRSS was found in 42% of patients who had less FVC decline ( $p=0.011$ ) and better HAQ ( $p=0.006$ ), compared with non-improvers. Cardiac involvement was less in mRSS improvers ( $p=0.008$ ), as well as progression in any internal organ ( $p=0.004$ ), and multiple internal organ progression ( $p=0.017$ ) at 1 year. Those with mRSS improvement showed a correlation between the degree of improvement and improvement in total disease severity ( $p=0.005$ ). Conclusion: High initial mRSS was linked to severity of joint contractures, worse function and quality of life, but was not predictive of visceral disease progression over a year. mRSS improvement was indicative of less frequent progression of internal organ involvement, less severe disease and improved HAQ.

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## Long-term Outcome of Patients with Systemic Sclerosis: Predictors of Organ Damage using Trajectory Models in a Large Canadian Scleroderma Inception Cohort

Leah Sinai, Tatiana Nevskaya, Mianbo Wang, Murray Baron, Janet Pope.

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Objectives: To study the course of internal organ damage over time in systemic sclerosis (SSc) patients using an inception cohort longitudinal design to identify damage trajectories. Methods: SSc patients from the CSRG database who had disease duration  $< 5$  years and follow up data available were included. Outcome was the trajectory of internal organ damage over time. Latent class mixed models were fitted with the package "lcmm" in R 3.2.0. A lower Bayesian Information Criteria value indicated a preferred model. Results: Three main damage trajectories were identified in 305 SSc patients. Compared to the most favorable trajectory, SSc patients with rapid accumulation of damage had active disease at baseline visit (100%), shorter duration from onset of Raynaud's phenomenon to diagnosis, more often dcSSc subtype, higher initial skin involvement with a rapid skin thickness progression rate prior to first visit, anti-RNAPol3, high rate of malignancy, more severe musculoskeletal involvement at first visit, severe renal disease. The best predictors in the final model of rapid damage trajectory were FVC $< 70\%$ , younger age of onset [45-54 years], renal involvement and tendon friction rubs (all  $p < 0.01$ ). Two other damage trajectories differed by the prevalence of either inflammatory manifestations, or internal organ involvement. They showed different rate of progression within the first years but reached similar level of organ damage in long-term. Conclusion: SSc patients can be classified into three main damage trajectories based on the pace of visceral damage accumulation over disease course, that can be predicted in early stage of disease.

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**Improving Pulmonary Utilization**      **Chronic Disease**      **Obstructive Action Plan**

**Michael Nicholson**, William Reisman, Inderdeep Dhaliwal, Alan Gob, Alia Kashgari.

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide representing an increasing economic and social burden. COPD, in Ontario in 2015, accounted for 24% of overall hospital admissions, the highest rate of hospital admission among major chronic illnesses in Canada. Inpatient Respiratory services established a COPD navigator who collaborates with a multidisciplinary team to facilitate a transition to home care. COPD action plans have been utilized to provide patients with easily accessible information for patients about their disease and possible treatments. The 2017 Global Obstructive Lung Disease (GOLD) guidelines suggest that Group C and D patients, including all admitted COPD exacerbation patients, should possess a written action plan. At London Health Science Centre (LHSC), Victoria campus, this action plan is completed by the COPD care navigator, nursing staff, and medical team; although standardized written action plans had not been utilized routinely. As a quality improvement measure, baseline data collection was performed discharged COPD exacerbation patients from May 1st to September 1st, 2017 via chart review focusing on documentation of an action plan being created, oral or written. Initial results revealed that only 27% of patients had formal documentation of action plan discussion. A quality improvement strategy was created to increase the percentage of patients receiving a formal action plan. Therefore, an easily accessible, electronic medical record-linked action plan was utilized and integrated into the admission care set for COPD. This was implemented on November 6th 2017. Currently an interim analysis is pending.

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**A Clinical Prediction Model for Raised Intracranial Pressure in Patients with Traumatic Brain Injuries**

**Pace, J**, Parry N, Vogt K, Hilsden R, Leeper R, Markova Z, Priestap F, Younan J, Ball I.

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Background Therapies for traumatic brain injury largely focus on limiting the progression of injury. Intracranial hypertension is believed to contribute to secondary brain insult. Currently the diagnosis of intracranial hypertension requires invasive monitoring or radiographic imaging. The aim of this study was to identify clinical variables associated with raised intracranial pressure prior to the completion of neuroimaging. Methods We performed a retrospective cohort study of head injured patients over a 3-year period. Patients were labelled as having increased ICP if they had a intracranial pressure >20 mmHg within 1 hour of monitor insertion or CT findings suggestive of raised ICP. Patient and clinical characteristics were analyzed using stepwise multivariable logistic regression with ICP as the dependent variable. Results Of the 701 patients identified, 580 patients met inclusion criteria. Mean age was 48.65 ± 21 years, 73.3% were male. Overall mortality was 14.7%. 46 patients had an ICP monitor inserted, however a total of 107 patients met the definition of raised ICP. The mortality rate for patients with raised ICP was 50.4%. Independent predictors of raised ICP were; age >55 (OR 2.26 ; 95% CI 1.35-3.76), pupillary fixation (OR 5.76; 95% CI 3.16-10.50), signs of significant head trauma (OR 2.431; 95% CI 1.39-4.26) and need for intubation (OR 3.589; 95 % CI 2.10-6.14). Conclusion This study identified four independent variables associated with raised ICP and incorporated these findings into a preliminary risk assessment scale that can be implemented at the bedside to identify patients at significant risk of raised ICP.

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## Acceptability of Fecal Microbial Transplantation Among Non-Alcoholic Fatty Liver Disease Patients

Justin Tat-Ko, Melanie Beaton, **Seema Parvathy**, Karim Qumosani, Laura Craven, Jeremy Burton, Adam Rahman and Michael Silverman.

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**BACKGROUND:** Fecal Microbial Transplantation (FMT) has been used successfully to treat recurrent *Clostridium difficile* infections, and has a patient acceptability rate of over 90%. However, the acceptability of FMT as a potential therapy for Non-Alcoholic Fatty Liver Disease (NAFLD) is unknown. The aim of this study was to gauge the acceptability of FMT among NAFLD patients, a population that may benefit from this therapy.**METHODS:** A questionnaire was administered to adult patients attending a tertiary care hepatology clinic for NAFLD follow up from June 2016 to October 2017.**RESULTS:** Two hundred fifty patients were approached with 101 patients completing the questionnaire. These patients had a mean age of 52 years [Range 18-76, SD 14.5] and a mean BMI of 34 [Range 18-58, SD 7.4]. Patients who had a higher BMI were more likely to accept the FMT ( $P<0.05$ ), but sex and post-secondary education were not significantly correlated with acceptance. Acceptance of FMT was 81% (82/101) by oral capsule, via colonoscopy 52% (53/101), duodenoscopy 54% (54/101) or enema 42% (42/101). Nineteen percent (19/101) of patients had treatment concerns, with 63% (12/19) of them reporting that it was unappealing. However, 90% (91/101) of patients agreed to consent to the FMT if data suggested that it would improve their condition.**CONCLUSION:** FMT was considered as a potentially acceptable therapeutic modality by the majority of NAFLD patients. However, a subgroup of patients found it unappealing, as the modality of administration may be affecting acceptability. Further studies in other patient groups would be helpful.

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## A Single Centre Randomized Control Trial of Intravenous Lidocaine for the Management of Traumatic Rib Fractures

**Dr Petrease Patton**, Dr. Ian Ball, Dr. Kelly Vogt, Dr. Arjun Kundra, Dr. Lauren Zarnett, Fran Priestap.

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**Introduction:** Traumatic rib fractures (RF) are a relatively common occurrence in patients of all ages, with a 10% incidence in all trauma patients and are associated with significant morbidity and mortality. Adequate analgesia is paramount for preventing the sequence of pulmonary complications and can reduce morbidity and mortality. There is longstanding evidence of lidocaine's effectiveness and safety in the post-operative patient and we hypothesize that this modality may prove to be ideal in trauma patients with RF. Therefore, it is imperative that intravenous lidocaine be investigated to ascertain if there is significant benefit for pain reduction in patients who have sustained RF.**Methods:** A single-centre, double-blind, randomized control trial to evaluate the analgesic efficacy of a 72-96 hour IV lidocaine infusion plus standard analgesics versus placebo plus standard analgesics will be performed on adult patients diagnosed with two or more RF from blunt thoracic trauma, requiring hospital admission at Victoria Hospital. **Outcomes:** The primary outcome is mean pain score, as measured on the Visual Analog Scale (VAS). Secondary outcomes are protocol adherence, patient satisfaction (measured on VAS), incidence of respiratory failure requiring mechanical ventilation, hospital length of stay (LOS), ICU LOS, mortality, incidence of lidocaine toxicity, treatment regimens (use non-opioid analgesics) and total morphine equivalents used. **Rationale:** This trial will serve to quantify the analgesic efficacy of intravenous lidocaine for patients with traumatic rib fractures. Successful completion this trial will inform the development of a multicentre trial powered to demonstrate a reduction in respiratory failure in the trauma population.

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### **Who's the Faller? Gait Performance When Approaching an Obstacle Identifies Elderlies Who Fall: Results from The "Gait and Brain Study".**

**Frederico Pieruccini-Faria**, Manuel Montero-Odasso.

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Background: Falls in elderlies frequently occur when walking forward during obstacle negotiation situations. However, it is currently unknown whether elderlies at higher risk of falling (Fallers), compared with low risk (Non-fallers), have worse gait performance when approaching an obstacle. Aims: The primary aim of this study was to compare gait performance between Fallers and Non-fallers during usual gait (unobstructed) and when approaching an obstacle (obstructed). The secondary aim was to determine diagnostic accuracies of gait parameters to identify Fallers. Methods: 137 non-demented elderlies were enrolled (72.2 ±5.1 years of age; 60.6 % of women). Fallers (n=26) were elderlies who had at least one injurious fall or at least two non-injurious falls during the last 12-months period. Participants performed gait assessments under unobstructed and obstructed conditions. During the obstructed condition participants walked and stepped over an obstacle set at 15% of participants' height transversally placed on a 6-meter electronic walkway. Gait speed and step-to-step variabilities were quantified from the last six steps prior to obstacle crossing. ANOVAs investigated interactions between groups and conditions adjusted for confounders. The area under the receiver operating characteristic curve (AUC) determined diagnostic accuracies of gait parameters. Results: Fallers had disproportional increase in step length variability from unobstructed to obstructed condition compared with Non-fallers (p=0.005). Step length variability demonstrated the best sensitivity/specificity diagnostic trade-offs (AUC = 0.64; p=0.03). Conclusion: Gait stability in Fallers is disproportionately disturbed when approaching an obstacle and is useful to identify elderlies at high risk of falls.

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### **Mitochondrial Dysfunction and Programmed Cell Death Pathways in Ischemia/Reperfusion Injury**

**Adnan QAMAR**, Ingrid GAN, Jieping GONG, Xuyan HUANG, Anthony JEVNIKAR, Zhu-Xu ZHANG.

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Inhibition of cell death has tremendous potential for the management of diseases characterized by ischemia/reperfusion injury (IRI) and in organ transplantation. However, effective clinical management strategies are lacking due to inadequate understanding of the cell death mechanisms. Endothelial cells (ECs) are critical mediators of organ dysfunction in IRI. Our data indicates that inhibition of caspases in ECs during hypoxia decreases apoptosis but increases necroptosis – a programmed form of necrosis. The major death effector complex of necroptosis, the necrosome, translocates to the mitochondria and induces mitochondrial dysfunction which triggers the downstream pathways of necroptosis. IRI itself significantly alters mitochondrial metabolism and permeability. In the present study, we wish to explore how mitochondrial dysfunction in IRI influences cell death pathways. To evaluate the effects of IRI, EC cultures will be incubated under various hypoxic conditions. TNF $\alpha$  and IFN $\gamma$  will be added to induce cell death. Various inhibitors will be used to suppress the activity of key molecules involved in the downstream pathways of necroptosis and apoptosis. Cell death will be quantified and classified using real time imaging and flow cytometry. Our data indicates that necroptosis plays a significant role in hypoxia induced EC death. We will be further investigating how mitochondrial dysfunction and altered permeability during IRI influences cell death pathways and the specific roles of various mitochondrial mediators in inducing cell death. We believe that understanding of these cell death pathways is critical in formulating clinically applicable therapeutic and preventative strategies aimed at reducing cell death in diseases characterized by IRI.

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## **Identifying Factors Associated with Coagulated Bone Marrow Aspirates**

**Dr. Mike Radford**, Malcolm Blagrove, Dr. Cyrus Hsia, David Hudson, Dr. Alejandro Lazo-Langner.

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**Background:** Completing a bone marrow aspiration (BMA) for diagnostic purposes is required for a wide array of pathologies. One potential complication with the procedure can be the sample coagulating and becoming inadequate for evaluation. There is minimal literature documenting the rate of coagulation of BMA samples or identifying factors predisposing samples to coagulation. **Objective:** Evaluate incidence of coagulated BMA samples and their associated factors. **Design:** BMA samples were retrospectively determined to be clotted/not clotted. For each BMA, factors captured included: Location, setting, body habitus, clinical service collecting the BMA, level of experience of health care professional, disease, antiplatelet and anticoagulants patient is on, body site BMA obtained from, patient positioning, and comorbid hypercoagulable states. **Results:** 2550 total BMA samples were obtained. A total of 2072 BMA samples were included. 1795 BMA samples were adult and 277 samples were pediatric. 3.28% (2.60-4.14%) of samples were clotted (68/2072), 60 adult samples and 8 pediatric samples. Of the adults with clotted BMA samples, 5 patients had 1 repeat bone marrow aspiration and 1 patient had 2 repeat marrows. Of the pediatric patients with clotted samples, 1 patient had 1 repeat marrow. **Conclusion:** It is believed that coagulation of BMA samples occurs at an appreciable rate. Of the factors compared between coagulated and non-coagulated samples, none were of clinical significance.

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## **Role of serum erythropoietin level measurement in the diagnosis of Polycythemia Vera patients**

**Sheikh Rahman**, Dr Cyrus Hsia (main supervisor), Dr Selay Lam, Dr Alan Gob, Dr Mangel Joy, Dr Martha Louzada, Dr A. Lazolanger.

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**BACKGROUND:** Polycythemia vera (PV) is one of the myeloproliferative neoplasms characterized by clonal expansion of a hematopoietic progenitor, erythrocytosis, often with leukocytosis and/or thrombocytosis. 90 to 95 percent of patients have an activating mutation in Janus kinase 2 (JAK2). The symptom burden ranges from pruritus to small or large vessel thrombosis, splenomegaly, severe fatigue, cardiovascular complications and a chronic risk of disease transformation to myelofibrosis or acute myeloid leukemia. The 2016 World Health Organization (WHO) criteria for the PV diagnosis include three major criteria, and one minor criteria which is subnormal serum erythropoietin level. According to the WHO guideline, patients can be diagnosed with PV with normal or even increased serum erythropoietin level (secondary to other comorbidities) if they fulfill all three major criteria. Early PV diagnosis is essential to control the complication associated with it. In this retrospective study, data will be collected from reviewing all the charts of each patient. We will include JAK2+ PV patients followed for at least 6 months in clinic and who received HU therapy. We will exclude the patients with any severe terminal illness preceding the diagnosis of PV that was likely to result in death within the year and patients not seen at least once yearly in clinic. **OBJECTIVES:** Our primary aim is to assess the value and level of serum erythropoietin in the diagnosis of PV. Study currently in progress.

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## **Prevalence of Thrombophilia in Suspected Stroke Patients**

**Omar Raslan**, Christopher Tran, Luciano Sposato, Alejandro Lazo-Langner.

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In our center, we have received around 500 thrombophilia screening requests for patients thought to have an ischemic stroke / Transient ischemic attack (TIA). This routine thrombophilia screening may over exaggerate the potential causality between stroke and thrombophilia; and may also pose more risk than benefit to stroke patients, in terms of overtreating otherwise stable

patients. Also, from an economical stand point, each screening test, costs around 600 CAD\$ per panel, which can be a huge financial burden if it becomes more routinely adapted in day-to-day practice, without any actual clinical benefit. We are performing this retrospective cohort study to measure the prevalence of thrombophilia in our patient population, and as a result, the usefulness of its routine screening.

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### **Clinical characteristics, microbiology, and outcomes of first episode infective endocarditis in injection drug users versus non-users.**

**Laura Rodger**, Michael Silverman, Stephanie Dresden, Glockler-lauf.

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Injection drug users (IDUs) with infective endocarditis represent a distinct and growing demographic of patients. We sought to identify clinical characteristics in first episode IE in IDU and non-IDU patients and compare clinical features, outcomes and treatment strategy. This was a retrospective chart review of adult inpatients between February 2007-March 2016 in two tertiary care hospitals in London, Ontario. All patients were diagnosed with first episode infective endocarditis (definite cases per Modified Duke's Criteria). Outcomes included all cause mortality, causative organism, site of infection, complications, and surgical management in drug users and non-drug users. In 376 first episode cases, 53.9% occurred in IDUs. These patients were younger ( $35.4 \pm 9.96$  vs  $59.44 \pm 14.85$ ;  $p < 0.001$ ) and more likely to have right-sided infection (17.1, 95% CI 9.49-32.9;  $p < 0.001$ ) caused by MSSA (4.37, 95% CI 2.80-6.94;  $p < 0.001$ ) or MRSA (2.81, 95% CI 1.52-5.43;  $p < 0.01$ ). In total, 36.5% of patients were treated surgically with IDU patients less likely to undergo surgery (0.18, 95% CI 0.11-0.29;  $p < 0.001$ ). Higher all-cause mortality was associated with age (1.83, 95% CI 1.05-3.20;  $p = 0.03$ ), aortic valve (2.99, 95% CI 1.62-5.52;  $p < 0.01$ ) or mitral valve infection (2.72, 95% CI 1.55-4.79;  $p < 0.01$ ). Mortality decreased with surgical treatment (0.39, 95% CI 0.22-0.69,  $p < 0.001$ ) and IDU (0.41, 95% CI 0.20-0.83;  $p < 0.0001$ ). We identify important clinical differences between IDUs and non-drug users with respect to valve involvement,

causative organism, associated comorbidities which have important management implications.

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### **The Effectiveness and Safety of Dalteparin Use in Quotidian and Nocturnal Hemodialysis Patients.**

**Rammdeep Saini**, Muirhead NC, Lindsay RM, Louzada M, Keeney M, Huang SHS..

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**Introduction:** Low-molecular-weight heparin, such as dalteparin, is an alternative anticoagulation method in conventional hemodialysis (HD). However, there are limited studies on its use in quotidian and/or nocturnal HD. We assessed the optimal dose, efficacy, and safety of dalteparin in quotidian and nocturnal HD populations. **Method:** This study included 10 quotidian (6 in-centre and 4 home) and 6 nocturnal home HD patients. Dalteparin was initiated and titrated based on clotting score. Trough anti-Xa levels were measured. The dalteparin dose, the dialyser and HD circuit clotting scores, and bleeding episodes were recorded at 1 month. Patients who continued dalteparin were followed to 12 months. **Results:** For the 10 quotidian patients, the median dalteparin dose was 2500 units/treatment. One patient died due to an unrelated cause. One patient withdrew from the study. For the 6 nocturnal patients, the median dose was 7,500 units/treatment. Three nocturnal patients discontinued dalteparin due to high clotting scores. For all patients who continued on dalteparin, only 9% of the HD treatments had clotting scores  $> 2$  after reaching stable dose. All trough anti-Xa levels were  $< 0.1$  IU/mL. No patients experienced bleeding. 11 patients continued dalteparin after 1 month. After 1 year, none had significant bleeding episodes except 1 quotidian patient who experienced bruising. **Conclusion:** This important pilot study has demonstrated the effectiveness and safety of dalteparin in quotidian HD. However, its use in nocturnal HD was only successful in 50% of patients. Alternative methods, including second dalteparin bolus after 4 hours of treatment, should be assessed for efficacy.



## **Quantitative Analysis of LHSC's 'Mortality Review Form' within the Department of Medicine**

**Michael Sattin**, Kathryn Myers.

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**BACKGROUND:** In an effort to identify opportunities to improve care, LHSC developed a 'Mortality Review Form' (MRF) for mandatory completion by the MRP on Medicine inpatients. The MRF includes a 5-category classification of death ("anticipated" to "unexpected"), a section for comments, and 6 quality indicators: critical incidents(CI), delays in care, in-hospital infections, in-hospital complications, medication errors, and other issues. **OBJECTIVE/METHODS:** Data collected on 1306 MRFs from November 2015 to January 2018 was extracted and anonymized prior to analysis. The proportion of deaths in each category was assessed and thorough analysis undertaken for unanticipated deaths. The six quality indicators were analyzed for trends. **RESULTS:** Of the 1306 deaths, 211 (16.2%) did not have a MRF completed by the MRP. Category 1 and 2 deaths accounted for 95.5% of the total deaths, with 14 total CI (77.8%). Only 49 deaths were reported as 'unexpected' (categories 3, 4, 5), and these accounted for 22.2% of CI. Of completed reviews there were 14 (1.3%) delays in care, 12 (1.1%) in-hospital infections, 34 (3.1%) in-hospital complications, 2 (0.2%) medication errors, and 29 (2.7%) other issues. Twelve deaths reported as having no identifiable issues were still reported as a result of CI, accounting for 66.7% of total CIs. **CONCLUSION:** MRPs identified very few deaths as unanticipated. CIs appear to be interpreted variably by MRPs as they were distributed between all categories of death. The low incidence of other quality indicators may have resulted from a lack of clarity about the purpose of the form.

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## **Rate and Timing of Renal Biopsy Complications**

**Melissa Schorr**, Andrew House, Matthew Weir.

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**Background:** Renal biopsy is an invasive test with significant risk for complications. Most complications are thought to occur within the first 8 hours post-procedure though monitoring duration is highly variable. **Objectives:** To determine the rate and timing of complications from renal biopsy, risk factors for complications, and the ideal post-biopsy monitoring duration. **Methods:** A retrospective chart review of renal biopsies performed from 2012 to 2017 comparing risk factors, rate and timing of complications. Minor complications included perinephric hematoma, hematuria or bleeding not requiring treatment; major complications included bleeding requiring transfusion; serious complications included requirement for surgical or radiologic intervention or death. IBM SPSS 25 was used to perform univariate analyses and exploratory logistic regression. **Results:** 617 biopsies were performed during the study period: 357 inpatient and 260 outpatient; 246 native kidney and 368 transplant biopsies. Complications occurred in 79 patients (12.8%) of which major and serious occurred in 12 (1.9%) and 2 (0.3%) patients respectively. Lower pre-procedure hemoglobin and platelets, higher degree of proteinuria, older age and lower BMI were associated with increased risk of complications in univariate analysis. Hemoglobin, proteinuria and BMI remained significant in multivariable analysis. 91% of all complications were detected immediately; 95% were detected within 4 hours of the procedure. **Conclusions:** In our centre, the rate of all complications from renal biopsy is 12.8% with a risk of 1.9% major and 0.3% serious, which is consistent with the literature. The majority of complications were recognized immediately. Ideally, patients should be monitored for 4 hours.

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## **Multi-dimensional assessment in idiopathic pulmonary fibrosis**

**Hana Serajeddini**, Marco Mura, Paola Rogliani.

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**Background.** The pathophysiology of idiopathic pulmonary fibrosis (IPF) is complex, and its clinical course is difficult to predict. Perceived dyspnoea, exercise capacity, and lung physiology have all been associated with mortality outcomes in IPF, but the significance of

these relationships is unclear. We sought to investigate the correlation among these variables and their independent predictive capability in determining mortality outcomes. **Methods.** Four-hundred-thirty-seven patients diagnosed with IPF from 3 independent centres were included. Medical Research Council dyspnoea score (MRCDS), 6-minute walk distance (6MWD) and pulmonary function tests were determined at baseline. The main endpoint was 18-month transplant-free survival. **Results.** Correlations between MRCDS, 6MWD, FVC and DLCO were either very weak or weak ( $r < 0.5$ ). The calculation of variance inflation factors demonstrated absence of collinearity among these variables. At the end of the observation period, 165 patients were alive, 167 had been transplanted, and 105 had died. Univariate regression analysis and c-statistics identified MRCDS (H.R.=1.89, area under the curve [AUC]=0.74), 6MWD (H.R.=0.97, AUC=0.79), FVC (H.R.=0.97, AUC=0.76) as significant predictors of 18-month survival. Multivariate regression analysis retained MRCDS (H.R.=1.33), 6MWD (H.R.=0.98) and FVC (H.R.=0.99) as independent predictors of mortality. **Conclusion.** In patients with IPF, baseline perceived exertional dyspnoea, exercise capacity and lung function are weakly correlated to each other, translating into low collinearity. MRCDS, 6MWD and FVC are significant and independent predictors of outcome, suggesting that a multi-dimensional assessment of IPF is appropriate and advantageous from a prognostic point of view.

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### **Applicability of the 2016 American Society of Echocardiography diastolic function guidelines in patients with heart failure with preserved ejection fraction**

**Olusegun Sheyin, MD, FRCPC**, Tahseen Rahman, MD, FRCPC, Shahrukh Bakar, MD, FRCPC, David McCarty, MB, BCh, MRCP(UK), Ryan Davey, MD, FRCP, FACC, Stuart Smith, MD, FRCPC, Robert McKelvie, MD, PhD, FRCPC, Sabe De, MD, FRCPC, FASE.

**Background:** There is no published data on the applicability or prognostic significance of the updated American Society of Echocardiography (ASE) diastolic function guidelines in patients with

heart failure with preserved ejection fraction (HFpEF). **Methods:** We performed a retrospective cohort study of consecutive HFpEF patients referred to the heart failure clinic from October 2015 to April 2017. Baseline characteristics were obtained, and diastolic function was assessed for each patient using the 2016 ASE guidelines. The primary outcome of the study was all cause mortality or heart failure hospitalization. The secondary outcomes were the individual components of the primary outcome and the number of HF clinic visits. **Results:** 50 subjects, with mean age of  $75.5 \pm 12.1$  years were included. 36% of the subjects were men and the mean LVEF was  $61.5 \pm 7.5$ . 28% of subjects had grade 2 diastolic dysfunction, while 2%, 18% and 24% had grades 1, 3 and indeterminate diastolic dysfunction, respectively. The diastolic function grade could not be assessed in 22% of patients. Grade 2 diastolic dysfunction was associated with worse outcomes; however, this finding was not statistically significant. The indeterminate diastolic function group was associated with a statistically significant increase in the number of heart failure clinic visits when compared with the normal diastolic function group ( $p = 0.000391$ ). **Conclusion:** The feasibility of the 2016 ASE guidelines in classifying diastolic dysfunction in patients with HFpEF was only 78%. Our study suggests that patients with indeterminate diastolic function have a worse prognosis than patients with normal diastolic function.

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### **Role of inflammation in Dclk1+ cell-derived colitis-associated colon cancer**

**Alice E. Shin**, Elena N. Fazio, Hayley J. Good, Liyue Zhang, Philip M. Sherman, Timothy C. Wang, Samuel Asfaha.

Colorectal cancer (CRC) is the second leading cause of cancer death in Canada, with the major risk factor being chronic inflammation. However, how inflammation leads to cancer is not well understood. We previously showed that Dclk1, a commonly used marker of tuft cells, labels long-lived quiescent cells that serve as a cellular origin of CRC upon dextran sulfate sodium (DSS)-induced inflammation. Therefore, we aim to determine the generalizability of inflammation-induced tumorigenesis and explore the

mechanism by which inflammation induces tuft cell cancer initiation. We hypothesize that colonic inflammatory insults lead to dedifferentiation of Dclk1+ tuft cells to a stem cell state susceptible to tumor initiation. We generated tamoxifen-inducible Cre transgenic mice that allow for Dclk1+ cell lineage tracing and cell-specific knock-out of the tumor suppressor adenomatous polyposis coli (APC) (Dclk1/APCfl/fl). Following tamoxifen induction, mice were administered various colitis-inducing agents. To examine the role of dedifferentiation in tumorigenesis, we ablated intestinal stem cells (ISCs) post colitis in our Dclk1/APCfl/fl tumor model. Treatment with DSS, TNBS, oxazolone, or Citrobacter rodentium induced colonic inflammation as detected by significantly increased myeloperoxidase (MPO) activity and histologic analysis. Surprisingly, development of colonic tumors was specific to DSS-induced colitis. Interestingly, ablation of ISCs post colitis significantly reduced colonic tumors in Dclk1/APCfl/fl mice. Our data suggests that an inflammatory response unique to DSS colitis results in transformation of Dclk1+ tuft cells and colonic tumor formation, and this appears to be mediated through Lgr5+ cells. These findings provide insight into the mechanisms by which Dclk1-derived colonic tumors arise.

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### **The Effect of Acute Rejection and Cytomegalovirus Infection after Transplantation on the Development of Pneumocystis Pneumonia (PCP) in Solid Organ Transplant Recipients: A Multi-Center Case-Control Study**

**Mostafa Shokoohi, G Singh, S Dufresne, A Jevnikar, R Prasad, A Shoker, D Kabbani, M Hebert, H Cardinal, I Houde, A Humar, D Kumar, SM Hosseini-Moghaddam.**

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Background: Pneumocystis pneumonia (PCP) is associated with morbidity and mortality in solid organ transplant (SOT) recipients. We determined the risk factors of PCP in SOT patients using a case-control design. Methods: Eight transplantation centers participated. For each case (SOT recipient with PCP), 4 controls (SOT without PCP) were included. Controls were matched to the cases based on transplant center,

type of allograft and date of transplant ( $\pm$  6 months). Adjusted conditional logistic regression model was applied to assess the association between the main exposure variables including rejection, cytomegalovirus (CMV) infection, and PCP prophylaxis with PCP. Results: We enrolled 58 cases and 229 controls. Transplant types included kidney (n=223), liver (n=15), kidney-pancreas (n=14), heart (n=30) and lung (n=5). PCP occurred beyond 12 months after transplantation in 48 (82.8%) patients. Thirty-four patients (58.6%) required admission to ICU and 28 (48.3%) had mechanical ventilation. Allograft failure occurred in 21 (36.2%) patients and 15 (26.3%) died. No patient developed PCP prophylaxis breakthrough. The proportion of female sex, kidney dysfunction, congestive heart disease, diabetes mellitus, allograft rejection, CMV infection and severe lymphopenia were significantly higher in cases. In conditional logistic regression model, CMV infection (adjusted odds ratio (AOR): 5.4, 95% confidence intervals (CI): 2.2, 13.6) and allograft rejection (AOR: 4.6, 95% CI: 1.9, 11.1) significantly increased the likelihood of PCP. Conclusions: PCP was mostly a late-onset disease associated with significant allograft loss and mortality. Extended prophylaxis targeting recipients with graft rejection or CMV infection may reduce the risk of PCP.

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### **Addressing prolonged lengths-of-stay in the Urgent Medical Clinic using Lean Methodology**

**Erin Spicer, Genevieve Chick, Amena Ghumman, Nicole Hugel, Erik Van Oosten.**

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BACKGROUND: Appointments in the Urgent Medicine Clinic (UMC) are scheduled for 30 minutes (new consultation) or 15 minutes (follow-up), yet baseline data collection demonstrated an average length-of-stay of 74 minutes. Long clinics stays have negative consequences, including patient dissatisfaction. Other academic centres have successfully reduced clinic wait times using Lean methodology. METHODS: This Quality Improvement (QI) study was piloted in the UMC at Victoria Hospital, an academic tertiary centre in London, Ontario. The design was an uncontrolled prospective trial guided by Lean methodology. The ideal length-of-stay in the

UMC – called the Takt Time – was calculated based on a 4-hour clinic. Value Stream Mapping was used to identify waste in the current system and root cause analyses were conducted on each identified source of waste. Interventions were trialed according to the common QI framework, Plan-Do-Study-Act (PDSA) cycles. RESULTS: Based on value stream mapping, early PDSA cycles aimed to (1) reduce the time patients wait for resident assessment, (2) eliminate repeated tasks such as history taking by multiple healthcare providers, and (3) readily identify any discrepancy between documented referring physicians' reason for consultation and patients' self-identified concerns. The primary outcome, length-of-stay in the UMC, was displayed as a Statistical Process Control S-chart and analyzed for special cause variation. CONCLUSIONS: The use of Lean methodology identified numerous sources of waste that prolong length-of-stay in the UMC and highlighted targets to be trialed via PDSA cycles.

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### **Physician feedback and antibiotic prescribing patterns**

**Dr Gavin Sun, Dr Michael Silverman.**

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Background: Antibiotics have revolutionized modern medicine and have transformed infections with serious potential morbidity and mortality into eminently manageable and survivable conditions. However, in addition to the direct unnecessary costs from dispensing redundant therapy, inappropriate antibiotic prescribing incurs substantial indirect socio-economic costs related to the associated adverse side-effects and the promotion of the development of resistant organisms. Audit and feedback (A&F) when well designed, presented, framed and implemented, has been shown to be a cost-effective and efficacious tool in influencing physician behavior change. Objectives: Assess the impact of audit and feedback in antibiotic prescribing patterns. Methods: A literature review was conducted on Pubmed, searching for articles using the search terms "prescriptions", "prescribers", "antibiotic", "audit and feedback" and "inappropriate prescribing". Results: Four studies were identified for inclusion. An important distinction between effective and ineffective audit

and feedback interventions in antibiotic prescribing is related to the method and context of framing an individual physician's behavior. When framed in context, audit and feedback has been shown to decrease inappropriate antibiotic prescribing. Conclusions: As the gate-keepers to antibiotic prescriptions, targeting physician perception and behavior with A&F has been shown in American and British settings to be effective at altering prescribing patterns. Given the incidence of inappropriate antibiotic prescribing in Canada and consequent adverse socio-economic and medical outcomes, there is a need to alter Canadian physician antibiotic prescribing behavior. Audit and feedback is imminently applicable to the Canadian context and, if implemented well, would yield widespread and long-term societal benefit

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### **Induction of CYP2C9 in a poor metabolizer genotype**

**Dr Gavin Sun, Dr Steven Gryn.**

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BACKGROUND: Warfarin use is complicated by wide variability in dose response, partially due to genetic variation in CYP2C9 and VKORC1. Rifampin is an infrequently used antibiotic that strongly induces mediators of drug elimination, generally leading to subtherapeutic effect or need for significantly increased dose of co-administered drugs. METHODS: A 76 year old woman was referred to the Clinical Pharmacology Personalized Medicine service to recommend optimal anticoagulation therapy for stroke prevention due to atrial fibrillation, in the context of requiring rifampin for 3 months to treat a prosthetic joint infection. She had previously used warfarin, with a hypersensitive INR response, and was presently taking apixaban. Due to the rifampin interaction, warfarin was the preferred anticoagulant. Aside from collecting usual clinical data, blood was collected for pharmacogenomic testing for warfarin dose prediction. RESULTS: Pharmacogenomic analysis revealed she was both a poor metabolizer (CYP2C9 \*3/\*3) and sensitive to warfarin (VKORC1 A/A). A validated dose calculator predicted that in this rare combination, she would require 1 mg/day (not considering drug interactions), explaining her previous response to warfarin. The patient

ultimately required as much as 3mg daily to maintain therapeutic INR during the course of rifampin, which was largely uneventful and was switched back to apixaban upon completion. CONCLUSION: The CYP2C9 \*3/\*3 genotype is thought to have minimal function, so its induction was not expected to impact the warfarin dose requirement. This demonstrates that either \*3/\*3 has more enzymatic function than previously thought, or alternative pathways, when induced, can metabolize S-warfarin.

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### Identifying the role of G-Protein Signalling Modulator 3 in GPCR signalling

Anette A. Surmanski, Peishen Zhao, Alexey I. Pevererzev, Brad L. Urquhart, Peter Chidiac.

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G protein-coupled receptors (GPCRs) are the largest superfamily of cell surface receptors and serve as targets for over 30% of current pharmaceuticals. GPCRs activate G protein heterotrimers (GaGDP/GBY) by promoting GDP dissociation and GTP association. GPCR signalling is limited via G protein activity and interactions with B-arrestins. G Protein Signalling Modulator-3 (GPSM3) is a novel protein that influences receptor signalling by binding to inactive Gai-GDP, limiting GDP dissociation from Gai and also preventing Gai re-association to the GBY subunit. GPSM3 thus has the potential to prevent Gai-mediated signalling while prolonging GBY signalling. The objective is to determine whether GPSM3 inhibits GPCR signalling. Real-time bioluminescence-based kinetic assays for cAMP production and B-arrestin recruitment were used to study the effects of GPSM3 and mutants thereof on GPCR signalling in transiently transfected HEK-293H cells. GPSM3 overexpression inhibited basal and agonist-stimulated B-arrestin recruitment to Gai-coupled  $\alpha$ 2A-adrenergic and  $\mu$ -opioid receptors by 52% ( $p < 0.0001$ ), with no effect on recruitment to Gs- or Gq/11-coupled GPCRs. The effect of GPSM3 on  $\alpha$ 2A-adrenergic-B-arrestin diminished with partially inactive mutants of GPSM3 ( $p < 0.001$ ) and not observed with fully inactive mutants. In cAMP assays, GPSM3 reduced forskolin potency on endogenous HEK-293H adenylyl cyclase activity (LogEC50=-5.261) when compared with

control (LogEC50=-5.916), but the reason for this decrease is unclear ( $p < 0.0001$ ). The selective effect of GPSM3 on B-arrestin binding to Gai-coupled receptors is consistent with its greater affinity for Gai relative to other G protein subtypes, and suggests that G protein activation may be a necessary step in GPCR-B-arrestin recruitment.

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### Identification and Management of Cardiovascular Risk in Eosinophilic granulomatosis with polyangiitis

Shahna Tariq, Lillian Barra.

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Eosinophilic granulomatosis with polyangiitis (EGPA), an ANCA-associated vasculitis, is a systemic, chronic autoimmune disease commonly characterised by asthma, allergic rhinitis, and eosinophilia. Chronic inflammation is known to increase risk of cardiovascular disease (CVD) and a large portion of mortality in EGPA is attributable to CVD. In this single-centre chart review, we studied 21 patients with known EGPA to assess appropriate identification and management of cardiovascular disease risk factors. Mean age at time of diagnosis of EGPA was 59 years with an average follow-up time of 57.6 months. 71% were  $>50$  years of age at diagnosis and 48% of patients were male. 2 patients had atherosclerotic disease at diagnosis while 5 had cardiovascular involvement due to their EGPA. 10/21 (48%) had  $\geq 2$  modifiable traditional CVD risk factors at baseline. At most recent visit, 3 (14%) patients had developed new onset cardiovascular disease and all were on appropriate secondary prevention (anti-platelet/anticoagulant + lipid-lowering agent). For primary CVD prevention, sufficient information was available to calculate Framingham risk score in 9/17 (53%) at most recent visit. 7/8 (88%) were appropriately prescribed lipid-lowering therapy based on the 2016 Canadian Cardiovascular Society guidelines. During routine visits for EGPA, physicians are not sufficiently stratifying CVD risk, however, when identified, the majority of patients are placed on appropriate therapy.

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## **Retrospective review of pre-admission clinic notes to assess for delirium risk stratification in elderly patients.**

**Dr Dana Trafford, Dr Niamh O'Regan.**

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Objective: Delirium risk is often overlooked in pre-operative assessments, but is extremely common and leads to adverse outcomes post-operatively. Advanced age, cognitive impairment and history of delirium are known to significantly increase risk of post-operative delirium. This study aims to determine how often cognitive assessment and delirium risk are being considered in pre-operative older elective surgery patients. Methods: Using electronic health records, 100 LHSC preadmission clinic notes of patients aged  $\geq 80$  years were assessed for documentation of cognitive assessment and delirium risk factors. No assessments were excluded from the study. Results: We found that only 7 patients were counselled on delirium risk and only 3 assessments recommended delirium prevention measures. Of the 8 patients that were identified as having prior cognitive impairment or delirium, 7 patients were advised of their increased delirium risk post-operatively. Of the remaining 92 patients with no documented prior cognitive impairment, 11 were identified as having previous falls and/or considered "frail", but were not screened for cognitive impairment. In terms of other risk factors, although 34 patients were taking deliriogenic medications, polypharmacy was not addressed, in 53 patients no alcohol history was taken, and rates of neurological examination were low (15%). Conclusion: Our findings suggest that in this high-risk cohort of patients, delirium risk is being assessed sub-optimally. Given that delirium is now considered a preventable in-hospital complication, it is important that we develop methods to incorporate delirium risk stratification into pre-operative assessments and include information on delirium risk in the informed consent process.

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## **Preservation of treatment effects in non-inferiority trials**

**Michael Tsui, Brennan Kahan, Vipul Jairath.**

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Background: Non-inferiority trials are increasingly used to assess the effectiveness of new interventions. The aim of these trials is to demonstrate that a new intervention is not worse than an active comparator by preserving an adequate amount of the comparator's treatment effect. Objective: To evaluate whether non-inferiority trials adequately preserve the historical treatment effect of their active comparators. Methods: Data was extracted from 168 non-inferiority trials published in high impact medical journals with an impact factor  $>10$  between 2010 and 2015. Articles were assessed for whether they supported the effectiveness of the active comparator with prior randomized controlled trials or meta-analyses, and whether their non-inferiority margins were appropriate relative to the active comparator's previously demonstrated effect. Six trials included a placebo arm and were excluded from the analysis. Results: 15.4% (n=25) of trials provided definitive evidence for the effectiveness of the active comparator. In 8.6% (n=14) of trials, non-inferiority could be declared even if the new intervention was ineffective. In 56 trials with sufficient information for analysis, the median percentage of the active comparator's effect that was preserved by their margins was 54% (IQR, 21% to 67%), indicating almost half of new interventions could preserve less than half of the active comparator's effectiveness while still being declared non-inferior. Conclusions: The design of most non-inferiority trials in this review could allow erroneous declarations of non-inferiority, driven by the use of active comparators for which effectiveness had not been previously demonstrated and selection of inappropriately wide non-inferiority margins.

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## **Ibrutinib, dose dependently, promotes atrial fibrillation in mice by depressing cardiac conduction**

**Jari M Tuomi**, Loryn Bohne BSc, Robert Rose Ph.D, Anargyros Xenocostas M.D. and Douglas L. Jones Ph.D.

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Atrial Fibrillation (AF) is a side effect of ibrutinib, a first line therapy for the treatment of B lineage lymphoproliferative disorders. We performed in vivo intracardiac electrophysiological studies and high-resolution optical mapping of isolated atria to study AF inducibility and atrial electrical properties at different doses of ibrutinib. Mechanistically AF is commonly induced by factors promoting slowing of cardiac conduction or reduction in effective refractory periods (ERPs). We hypothesized that arrhythmia induction requires ibrutinib exposure in a dose dependent manner. C57BL/6 mice were orally administered ibrutinib (2 vs. 10 mg/kg) or vehicle. Intracardiac pacing induced AF following a single high dose (4/10 vs. 0/10,  $P < 0.05$ , duration  $36.6 \pm 56.5$  sec) but not low dose (0/10,  $P=1$ ) ibrutinib. A 24 hour washout reversed this effect even following chronic (14 day) high dose administration (2/8 vs. 2/8,  $P=1$ ). There was no change in ERPs. Optical mapping of isolated atria with 0nM, 10nM, 50nM, and following 30 min washout of ibrutinib was performed to determine conduction velocity (CV) changes. Atrial CV decreased with 50nM compared to 0nM (28.7 vs. 33.2 cm/s,  $n=5$ ,  $P < 0.01$ ) but not 10nM ibrutinib (31.7 cm/s,  $P=0.22$ ). A 30 min washout period restored the CV (32.5 cm/s,  $P < 0.01$ ). We demonstrated that ibrutinib acutely and dose dependently increased susceptibility to pacing-induced atrial arrhythmia in the mouse. Optical mapping showed this effect is likely due to slowing of cardiac conduction in a dose dependent and reversible manner. Altered dosing strategies may be sufficient to prevent this important side effect.

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## **Physician global assessments for disease activity in rheumatoid arthritis are all over the map!**

**Matthew Turk**, Janet Pope.

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Physician global assessments of disease activity (medical doctor (MD) globals) are important outcomes. MD globals may vary based on their age, gender, practice setting and experience (number of patients seen per year and years in practice). We determined the variability of MD globals, surveying rheumatologists from the Canadian Rheumatology Association using rheumatoid arthritis cases rated by MD for disease activity from 0 to 10. Cases were developed to span the spectrum of disease activity. Kappa, intraclass correlation (ICC) coefficients and linear mixed models were used. 109 responded to the survey (approximately 30% response). The range of MD globals for the same scenario was as high as 7.6 out of 10, indicating vast discrepancies between physicians. Some scenarios outlined changes in individual patients. Physicians often disagreed as to how much the patient recovered or worsened but agreed as to whether the patient improved or not. When physician-related factors were analysed separately, MD global scores were significantly influenced by age and experience (ranked by a physician, number of patients seen per year and years in clinical practice) in linear mixed models. Multivariate analysis revealed borderline significance for two age categories (56–65 years,  $P=0.049$ ; over 65 years,  $P=0.058$ ) and those who have seen 600–800 patients per year ( $P=0.056$ ). This work emphasizes the need to establish evaluation criteria in RA for disease. Perhaps, a catalogue of patient scenarios that range from 0 to 10 could be developed, standardised and agreed on to decrease the wide variability of ranking by rheumatologists.

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## **Comparison of Immature Platelet Fraction and q-SOFA as a prognostic measure for patients admitted with a suspected infection**

**Maggie Turnbull**, Cyrus Hsia, Mike Keeney, Wendy Brown, Ben Hedley, Ian Chin-Yee.

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Introduction London Health Sciences Centre (LHSC), and London Laboratory Services Group

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has recently acquired a Sysmex XN analyzer, which now allows us to accurately and efficiently measure immature platelet fractions (IPF) as a part of a complete blood count (CBC). Recent studies suggest that the percentage of IPF (IPF%) is associated with all-cause mortality in critically ill patients admitted with sepsis, but the prognostic value of IPF% has not been explored in a non-intensive care setting. The current prognostic tool for sepsis related mortality in non-critical patients, the q-SOFA score, lacks sensitivity and has only been validated as a late indicator of deterioration. A more reliable prognostic measure would be a clinical asset in these patients. Objectives To assess whether IPF% is a better predictor of mortality, ICU admission, or length of stay (LOS) than q-SOFA in patients being admitted to general medicine with a suspected infection. Methods A retrospective analysis that will compare the q-SOFA score, as measured by the emergency room vitals, with the IPF% for patients admitted under medicine at Victoria Hospital, LHSC. We will then perform a multivariate analysis to compare the two metrics. Results (pending) Conclusion (pending)

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### **Aluminum Toxicity from Exposure in an Auto Mechanic Shop - A Case Report**

**Erik M. van Oosten**, George Dresser.

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Introduction: Aluminum toxicity is rarely described in the literature, but typically occurs in the context of dialysis and renal patients. Herein is a report of a mild case of aluminum toxicity from exposure in an autobody shop. Case Presentation: A 51-year-old healthy male, who worked in an autobody shop, presented with vague symptomatology of episodic flushing, nausea, and paresthesias, persistent malaise, fatigue, tinnitus, myalgias, and diffuse weakness. He also complained of vague memory difficulties. Management & Outcome: Workup was unremarkable leading to a heavy metal screen. Serum aluminium was elevated (611 nmol/L; ULN = 222 nmol/L). The patient reported significant exposure to aluminum dust in his workplace. At the time of medicine assessment, serum aluminum level was repeated, and had dropped (345 nmol/L), with an elevation in response to

deferoxamine stimulation testing (371 nmol/L). Deferoxamine stimulation testing would be expected to cause a significant elevation in serum aluminum levels and is useful in establishing a diagnosis and guiding treatment. In one month follow-up the patient had resolution of symptoms, having taken measures to restrict aluminum exposure in the workplace by improving ventilation and enforcing use of appropriate face masks. Discussion & Conclusion: Aluminum toxicity is a rare systemic disorder with nonspecific symptoms. This report describes a mild case observed in a patient working in an autobody shop, a population in which it is worth considering aluminum toxicity as a diagnosis in cases of otherwise idiopathic nonspecific complaints. Diagnosis was confirmed with heavy metal testing and managed successfully with clinical observation and exposure control.

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### **Improving Control of Mineral Bone Disease in Peritoneal Dialysis Patients**

**Han Xiong Wang**, Ryan Marinovich, Robin Wigen, Nancy Woodcock, Arsh Jain, Elena Qirjazi.

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Introduction: Peritoneal dialysis (PD) patients often have difficulty regulating their calcium (Ca), phosphate (PO<sub>4</sub>) and parathyroid hormone (PTH) levels, placing them at risk for mineral bone disease (MBD). Following Ca/PO<sub>4</sub>/PTH trends is key in evaluating the effectiveness of different treatments. Hypothesis: The number of PD patients at our centre who meet targets for Ca/PO<sub>4</sub>/PTH levels can be improved by 5% within 9-12 months using quality improvement (QI) methodologies. Materials and Methods: We developed a simple tracking tool which includes: a) the trend of individual patients' Ca/PO<sub>4</sub>/PTH values and subsequent interventions, and b) a treatment guide for MBD. This tracking tool was used at our PD Unit starting in October 2017. The primary outcome is the change in the proportion of patients who meet all three targets, before and after implementation of our tool. Process measures include uptake of the tool by PD staff, number of Cinacalcet and parathyroidectomy referrals, and opinion surveys of stakeholders. Results: Baseline data indicates that 36.9% of our patients met targets for



Ca/PO4/PTH. 87.5% of respondents to an opinion survey felt the structure for MBD management is poorly defined and 56% believe that patient adherence is the biggest barrier. A chart audit done 2 months post implementation showed that the tracking tool was utilized in 11/13 PD clinics. 70% of patient charts had a completed tracking tool in it. Conclusion: We expect that our tool will help elucidate the trends of Ca/PO4/PTH and adapt MBD management for our patients, resulting in improved control within 9-12months.

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### **Reducing Overnight Non-Urgent Pages for On-Call CTU Residents**

**Darren Weaver, MD**, Dan Gillett MD, Andrew Appleton MD, FRCPC.

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**BACKGROUND:** Junior residents on the acute medicine Clinical Teaching Unit at London Health Sciences Centre have reported receiving pages overnight that they perceive to be non-urgent. If truly non-urgent, this interruption of workflow could adversely disrupt patient care. This may also impact residents' well-being by limiting rest during sleeping hours. **METHODS:** We studied the volume of overnight pages retrospectively between the hours of 12:00AM and 6:00AM. We then prospectively surveyed perceived urgency of pages received between 12:00AM and 6:00AM based on residents' opinions of whether a page needed to be dealt with immediately (urgent), or whether it could have waited until after 6:00AM (non-urgent). **RESULTS:** On average, residents received 6.2 pages between 12:00AM and 6:00AM, or roughly one page per hour. Pages were perceived to be non-urgent 43% of the time. **CONCLUSION:** Nearly half of the pages received by junior residents overnight may be non-urgent and safely held until after 6:00AM. Our next step is to investigate the content of pages deemed non-urgent, with the goal of implementing system changes to reduce the volume of non-urgent pages.

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### **Adherence to preoperative investigation ordering guidelines: an audit of practice**

**Dr. Sarah Weisz, Dr. Kathryn Myers.**

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**Background:**To inform preoperative investigative testing, guidelines were developed locally in 2015 based on patient characteristics, comorbidities and the risk of the planned surgery. As the first phase of a quality improvement study, we examined current ordering practices Preadmission Clinic (PAC) to determine adherence to our institution's guidelines. **Methods:**Over a one month period, we prospectively reviewed preoperative orders for patients referred to PAC. Exclusion criteria included patients undergoing transplantation or cardiac surgery, and those interviewed by telephone. Patient risk status was classified as low, medium or high by reviewing the preoperative patient questionnaire. Adherence to bloodwork, electrocardiogram and chest radiograph testing based on the preoperative risk-based testing guideline was analyzed. **Results:**Of 249 cases reviewed, preoperative testing was completely guideline adherent in only 24 (9.6%). Extra tests were ordered in 197 (79.1%), while recommended test were omitted in 28 (12.4%). INRs accounted for 182 of the 428 of extra blood tests ordered. ECGs were ordered in 56 patients who did not meet guideline requirements while 37 who required ECGs did not have one ordered. Chest radiographs, although not part of the guidelines, were ordered in 9 patients. **Conclusions:**Our prospective practice audit showed low adherence to locally-developed guidelines for preoperative test ordering. Possible explanations for these findings include inadequate dissemination and explanation of guidelines, or disagreement with the recommendations; the addition of INR measurement in over 40% of cases suggests the latter possibility. Future work will include interviews with key stakeholders to identify factors contributing to guideline nonadherence.

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## **Evaluation of Blast Cell Percentage in Myelodysplastic Syndrome by Flow Cytometry**

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**Introduction:** Percentage of bone marrow (BM) blasts is a critical prognostic factor in the International Prognostic Scoring System (IPSS) for myelodysplastic syndrome (MDS) and helps determine management of the disease. Morphologic evaluation is the established method of determining blast count but is subject to high interobserver variability. Flow cytometry (FCM) has been proposed as a useful tool to enumerate blast cells in MDS. We hypothesize that FCM is a more reproducible method of determining blast cell percentage in MDS compared to morphology. **Methods:** 38 BM aspirates from MDS patients underwent morphological review by 3 independent hematopathologists and FCM analysis by 2 independent operators. We then determined the correlation between the blast cell percentages obtained by the two methods. Furthermore, we analyzed interobserver agreement within each method using the intra-class correlation coefficient (ICC) and Bland-Altman plots. **Results:** We found that the average blast cell percentages obtained by FCM had a strong strong positive linear relationship to those obtained by morphology. The FCM method showed excellent interobserver agreement while the morphology method showed moderate agreement. The FCM method did not have a systematic bias for blast cell percentages compared to the morphology method. **Discussion:** Our findings show that FCM is a more reproducible method of determining blast cell percentage for prognosis of MDS. The clinical use of FCM to supplement morphologic evaluation should allow for more reliable prognosis and improved management of MDS.

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## **Levetiracetam and the risk of acute kidney injury: A population-based cohort study**

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**Background:** Regulatory agencies warn about the risk of acute kidney injury (AKI) with levetiracetam use. We conducted this study to determine whether new levetiracetam use is associated with a greater 30 day risk of AKI. **Study Design:** Population-based retrospective-cohort study. **Methods:** Adult patients in Ontario receiving a new outpatient prescription from January 2004 and March 2017 for levetiracetam were matched 1:2 to a cohort of levetiracetam non-users based on chronic kidney disease, seizure within 90 days, and a logit of a propensity score for levetiracetam use. The primary outcome was emergency visit or hospitalization for AKI within 30 days. Secondary outcomes were AKI at 90 days and 180 days. We assessed outcomes using health care diagnostic codes. In a subpopulation with laboratory measurements available, we evaluated changes in serum creatinine. **Results:** We successfully matched 3,980 patients with a median age of 59, receiving a new prescription for levetiracetam to 7,960 non-users. Levetiracetam use was not associated with a higher risk of AKI at 30 days (13 [0.33%] events in levetiracetam users and 21 [0.26%] events in non-users (relative risk, 1.24; 95% CI, 0.62-2.47). Relative risk for AKI at 90 days and 180 days were 0.92 (95% CI, 0.52-1.52) and 0.70 (95% CI, 0.43-1.13) respectively. Results from laboratory measurements were consistent with the primary outcome. **Conclusion:** In this population-based study, it is reassuring that levetiracetam use was not associated with a significantly higher risk for AKI.

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## **Determinants of readmission of patients discharged from an Acute Care of the Elderly Clinical Teaching Unit: A retrospective case-control study**

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**Background:**We examined factors associated with 30-day readmission following discharge from an Acute Care for the Elderly Clinical Teaching Unit (ACE-CTU) in London, Ontario.**Methods:**Demographic and admission-related factors were abstracted from selected charts of patients who were discharged from the ACE-CTU between October 1, 2013 and May 30, 2014 (n=727) in this retrospective case-control study (cases: emergency department/acute care readmissions within 30 days of ACE-CTU discharge; controls: no 30-day readmissions).**Results**The mean age of the 80 cases and 92 controls was 83.1 years; 61.0% were female. The odds ratios (OR) associated with early (0-7 days post discharge) and late readmission (8-30 days post discharge) were significantly greater among those experiencing incident delirium during their index admission (early readmission: OR (95% confidence interval (CI): 7.67 (2.67-22.06); late readmission: 4.86 (1.81-13.06) than those without incident delirium. Urinary catheterization and peptic ulcer disease were also significantly associated with both early and late readmission. Some factors impacted only early readmission (urinary tract infection (UTI): 3.44 (1.02-11.61); anti-psychotic use: 3.44 (1.02-11.61) or only late readmission (congestive heart failure (CHF): 3.23 (1.41-7.41); gastro-intestinal bleeding: 4.65 (1.62-13.32); chronic kidney disease (CKD): 2.66 (1.06-6.70).**Conclusions**Factors with both early and late impacts influence 30-day readmissions among patients discharged from an ACE-CTU. Findings reinforce the potential negative consequences associated with urinary catheterization or UTIs, and the importance of close post-discharge monitoring of patients with incident delirium, CHF, peptic ulcer disease, CKD, or gastro-intestinal bleeding, and/or those given anti-psychotic medications.

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