Research DAY 2016

Department of Medicine

GRADUATE STUDENTS | RESIDENTS | POSTDOCTORAL FELLOWS

Thursday May 19th, 2016

ORAL PRESENTATIONS

Classroom D, WMC 2F1.04

POSTER PRESENTATIONS

Lower Level

John W. Scott Health Sciences Library

Henri Matisse. *The Fall of Icarus*. 1946

Research DAY 2016
Department of Medicine

In 2015, members of the Department of Medicine contributed many peer-reviewed research papers to the literature, plus many scholarly reviews, book chapters, books and abstracts. The work spans the spectrum from molecule to patient and from patient to health systems. Research is central to what we do – it is the life-blood of medicine.

With some help from their supervisors, most of the Department's research work is actually done by residents, graduate students and postdoctoral fellows – and this work is showcased today. The Department of Medicine graduate program is one of the largest at this University with 78 graduate students and 30 postdoctoral fellows, and 230 residents are training in our core and subspecialty programs. Almost all of the trainees are involved in research at some level.

The trainees who are presenting the work today have put a lot of effort into their presentations, and many of them will take their findings to national and international conferences. You can help them by showing how much you value their effort, you can get a preview of what will be published by this Department in the near future, and by chatting with the presenters, you can add your ideas to this ongoing research. As is the case every year, the oral abstracts will be presented in Classroom D, and posters will be shown in the lower level of the John W. Scott Library (lunch is served). This year, I would like to welcome two guest adjudicators for the oral presentations:

Louise Pilote, MD, MPH, PhD, Director in the Division of General Internal Medicine at McGill University. She is a clinician-scientist in cardiovascular epidemiology, outcomes research and health services research and currently holds the James McGill Professorship Award.

Matthias Götte, MSc, PhD, Chair of the Department of Medical Microbiology & Immunology. Dr. Götte's research focuses on the study of viral replication and its inhibition.

Barbara J. Ballermann, MD

Table of Contents

Research Day Guest Oral Adjudicator

Louise Pilote, MD, MPH, PhD is the Director of the Division of General Internal Medicine and Professor in the Department of Medicine at the McGill University Health Centre (MUHC). Dr. Pilote received her medical degree from McGill University in 1985 and completed her internal medicine residency at the Royal Victoria Hospital in 1988. Dr. Pilote completed a Fellowship in Clinical Epidemiology (1990-92) and a Fellowship in Health Services Research (1992-94) at Stanford University. She also completed a postdoctoral fellowship (Cardiology; 1994-95) at the Cleveland Clinic. She has also received a Masters in Public Health at the Harvard School of Public Health (1989) and a PhD in Epidemiology at the University of California at Berkeley (1997).

Dr. Pilote's research interests include cardiovascular epidemiology, outcomes research and health services research. She has published 249 peer-reviewed publications in high impact Journals.

As a clinician-scientist, Dr. Pilote has an extensive teaching history with medical students and residents, supervising numerous medical residents, undergraduate, graduate students and postdoctoral fellows.

Dr. Pilote has attracted several million of dollars of funding during her academic career both from federal and industry sources. She has received a number of awards and currently holds the James McGill Professorship for a second term as an outstanding and original researcher of world-class caliber and an international leader in her field.

Research Day Guest Oral Adjudicator

Matthias Götte, PhD is Professor and Chair of the Department of Medical Microbiology & Immunology at the University of Alberta. Dr. Götte received his PhD in 1997 at the Max-Planck Institute in Martinsried, Germany. He completed his postdoctoral training at the McGill University AIDS Centre in Montreal from 1997-2000. His first academic appointment was in 2002 as Assistant Professor at McGill University in the Department of Medicine. His research interests include a broad range of important human pathogens, including HIV, hepatitis C virus and human herpesviruses. Research in his laboratory is focused on the study of viral replication and its inhibition. Emphasis is placed on structure-function relationships of viral polymerases and mechanisms involved in drug action and resistance with the ultimate goal to contribute to drug discovery and development efforts.

Dr. Götte has published approximately 97 peer-reviewed papers in high impact journals. He holds 3 patents and has attracted new investigator awards and multiple national grants from CIHR, Canadian Foundation for AIDS Research, CFI, Cancer Research Society, NSERC and industry.

Dr. Götte has directly supervised over 25 graduate students and postdoctoral fellows with almost all trainees securing external scholarships from CIHR and other agencies. He has served on a number of grant review panels for CIHR and NIH and has been editorial boards member and reviewer for a number of journals.

Meeting at a Glance

8:00-8:10	Welcome Address *(Dr. Evangelos Michelakis, Associate Chair, Research)* *(Dr. Barbara Ballermann, Chair)*
8:10–8:30	**Keynote Speaker** *(Dr. Louise Pilote)*
8:30-9:45	Oral Presentations
9:45-10:00	**Break**
10:00-11:15	Oral Presentations
11:00-1:00	Poster Presentations and **Lunch**
1:00-1:15	Translational Fellowship Award
1:15-2:30	Oral Presentations
2:30-2:45	**Break**
2:45-4:00	Oral Presentations
4:00	**Award Ceremony**

Morning Oral Presentations

Classroom D, 2F1.04 WMC

Time	Name		Title	Page
8:30	**Anmol Shahid** Supervisor: Sean McMurtry	GS	Mild Therapeutic Hypobaria Improves Left Ventricular Function after Acute Myocardial Infarction in Mice	22
8:45	**Candace Beilman** Supervisor: Brendan Halloran	GS	Early initiation of anti-TNF therapy is cost-saving compared to late initiation for patients with Crohn's disease	23
9:00	**Aris Boukouris** Supervisor: Evangelos Michelakis	GS	c-Myc 1 is reversibly induced by suppression of mitochondrial function	25
9:15	**Thomas Roston** Supervisor: Shubhayan Sanatani/Padma Kaul	GS	A novel mutation underlying an overlap between WPW syndrome, cardiomyopathy and sudden death	26
9:30	**Bruno Saleme** Supervisor: Gopinath Sutendra	GS	Metabolic Modulation as a Novel Therapy in Chemotherapy Induced Cardiotoxicity	27

9:45 Break

Morning Oral Presentations

Classroom D, 2F1.04 WMC

Time	Name		Title	Page
10:00	**Adam Kinnaird** Supervisor: Evangelos Michelakis	GS	THE VON HIPPEL LINDAU (VHL) TUMOR SUPPRESSOR INHIBITS P21 TO PROMOTE PROLIFERATION AND APOPTOSIS-RESISTANCE IN CANCER	29
10:15	**Michael Parkes** Supervisor: Philip Halloran	GS	NK Cell CD16α IgG Fc Receptors Are Activated in Antibody-Mediated Renal Allograft Rejection	30
10:30	**Manmeet Mamik** Supervisor: Christopher Power	PDF	Insulin Treatment Prevents Neuroinflammation and Neuronal Injury with restored Neurobehavioral Function in Models of HIV/AIDS Neurodegeneration	32
10:45	**Vivek Gandhi** Supervisor: Harissios Vliagoftis	GS	INSULIN REGULATES PROTEINASE-ACTIVATED RECEPTOR-2 EXPRESSION ON AIRWAY EPITHELIUM	33
11:00	**Emily Walker** Supervisor: Karen Goodman	GS	Community-Driven Research on Environmental Determinants of Gastritis Severity: Using Fish Intake as a Proxy for Mercury Exposure in Canadian Arctic Communities	34

11:15 Poster Sessions

Afternoon Oral Presentations

Classroom D, 2F1.04 WMC

Time	Name		Title	Page
1:00	Translational Research Fellowship Award Winner Presentation			
1:15	**Mohammad Rafaei** Supervisor: Cynthia Wu	CIM	Incidence of Catheter-related Thrombosis in Acute Leukemia patients: a comparative, retrospective study of the safety of Peripherally-Inserted vs. Centrally-Inserted Central Venous Catheters.	35
1:30	**ThucNhi Dang** Supervisor: Richard Fedorak	CIM	Efficacy of hepatitis B counseling and vaccination in patients with inflammatory bowel disease receiving anti-TNF therapy	37
1:45	**Selina Dobing** Supervisor: Jennifer Ringrose	CIM	Sleep quality, and factors influencing it, in the general medicine inpatient population	39
2:00	**Maryam Soleimani** Supervisor: Clarence Wong	CIM	Quality of Endoscopic Documentation in Cases of Barrett's Esophagus: A Retrospective Analysis	40
2:15	**Ghazi Alotaibi** Supervisor: Sean McMurtry / Cynthia Wu	CIM	Secular trends in incidence and mortality of acute venous thromboembolism: The AB-VTE population based study	42

2:30 Break

Afternoon Oral Presentations

Classroom D, 2F1.04 WMC

Time	Name		Title	Page
2:45	**Trevor Steve** Supervisor: Donald Gross	SSR	Histological validation of hippocampal subfield segmentation	43
3:00	**Vikram Gurtu** Supervisor: Evangelos Michelakis	SSR	Targeting Endoplasmic Reticulum Stress With 4-Phenylbutyrate Improves Mitochondrial Metabolism and Lung Function in Pulmonary Fibrosis	46
3:15	**Janek Senaratne** Supervisor: Sean Van Diepen	SSR	Routine Coronary Artery Bypass of Angiographically Borderline Coronary Artery Stenoses is not Associated with Improved Survival	47
3:30	**Ryan Stubbins** Supervisors: Anthea Peters	CIM	Prognostic Impact of CD3 Infiltrating T-cells in the Tumor Microenvironment with Clinical Factors for Solid Organ Transplant (SOT) Recipients with Post-Transplant Lymphoproliferative Disorders (PTLD)	49
3:45	**Peter Ao** Supervisor: Raj Padwal	SSR	Effect of Cuff Design on Auscultatory and Oscillometric Blood Pressure Measurements	50

4:00 **Award Ceremony (Bernard Snell Hall – Upper Foyer)**

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
1	**Abbas, Mariam** Supervisor: John Elliott	SSR	CONTACT ALLERGY TO THE TOPICAL ANESTHETIC PRAMOCAINE IS SURPRISINGLY COMMON AMONG PATIENTS BEING PATCH TESTED AT A TERTIARY DERMATOLGY CLINIC	51
2	**Abdualla, Radya** Supervisor: Nadia Jahroudi	GS	Correlation of aging with expression of thrombotic protein Von Willebrand Factor (VWF)	52
3	**Al Hamarneh, Yazid** Supervisor: Ross Tsuyuki	RA	The Alberta Vascular Risk Reduction Community Pharmacy Project: RxEACH	53
4	**Albalawi, Zaina** Supervisor: Finlay McAlister	GS	The impact of introducing an Enhanced Recovery After Surgery (ERAS) protocol in Alberta on individuals with diabetes: an interrupted time series analysis	54
5	**Alotaibi, Dhaifallah** Supervisor: Harissios Vliagoftis	GS	Lipopolysaccharide and Polyinosinic:Polycytidylic Acid attenuate Interleukin -13 induced Eotaxin-3	55
6	**Alotaibi, Ghazi** Supervisor: Sean McMurtry / Cynthia Wu	CIM	Short- and Long-Term Mortality after Pulmonary Embolism in Patients with and without Cancer	56
7	**Alzahrani, Khadija** Supervisor: Harissios Vliagoftis	GS	Cockroach Extract Down-regulates IL-13-Induced Eotaxin-3 mRNA Expression in an Airway Epithelial Cell Line	58
8	**Amin, Aditi** Supervisor: Vivian Huang	CIM	Effects of Metronidazole on Circulatory Dysfunction in Patients with Cirrhosis	59

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
9	**Amin, Aditi** Supervisor: Richard Fedorak	CIM	Using Infliximab Trough Levels and Fecal Calprotectin Levels Together to Guide Clinical Decisions has the Potential to Improve Outcomes in Inflammatory Bowel Disease Patients on Maintenance Infliximab Therapy	62
10	**Asahchop, Eugene** Supervisor: Chris Power	PDF	Antiretroviral therapy efficacy in the brain: a unique HIV-1 reservoir	64
11	**Bairwa, Suresh** Supervisor: Jason Dyck	GS	The effect of resveratrol-enhanced fecal transplant as a treatment for hypertension	65
12	**Basiuk, Morgan** Supervisor: Sunita Vohra	GS	Study of Natural Health Product Adverse Reactions in Cancer Patients: Preliminary Data in Adult Patients	66
13	**Blackmore, Derrick** Supervisor: Zaeem Siddiqi	GS	Optimization of IVIG Treatment for Neuromuscular Patients in Rural Areas of Northern Alberta	67
14	**Bohlouli, Babak** Supervisor: Scott Klarenbach	GS	Outcomes in CKD patients with hospital acquired complications	68
15	**Bohlouli, Babak** Supervisor: Scott Klarenbach	GS	Health care costs of hospital acquired complications in patients with CKD	69

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
16	**Boukouris, Aris** Supervisor: Evangelos Michelakis	GS	The Pyruvate Dehydrogenase Kinase Inhibitor Dichloroacetate enhances the antitumor activity of the Tyrosine Kinase Inhibitor Sunitinib in clear-cell renal cell carcinoma in vivo	70
18	**Chen, Xueyi** Supervisor: Gavin Oudit	GS	PI3Kβ has distinct role in endothelial cells and cardiomyocytes facing myocardial infarction	71
19	**Chenji, Sneha** Supervisor: Sanjay Kalra	GS	Social Cognition and Executive Functions in Amyotrophic Lateral Sclerosis	72
20	**Dang, ThucNhi** Supervisor: Lana Bistritz	CIM	Gastroenterology curriculum in the Canadian medical school system	73
21	**Dhesi, Sumandeep** Supervisor: Michelle M. Graham	SSR	Outcomes of Transfusions in Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: A Population Level Analysis	75
22	**Dimitry, Joseph** Supervisor: Dina Kao	GS	INDEPENDENT PREDICTORS OF FAILURE OF FECAL MICROBIOTA TRANSPLANTATION (FMT) FOR RECURRENT OR REFRACTORY CLOSTRIDIUM DIFFICILE INFECTION	77
23	**Dittrich, Alexandra** Supervisor: Karen Kroeker	GS	Assessing Sleep Quality in Patients with Inflammatory Bowel Disease Reporting Fatigue	79

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
24	**Du, Lillian** Supervisor: Richard Fedorak	CIM	The Within-Stool and Within-Day Variability of Fecal Calprotectin in Patients with Inflammatory Bowel Disease	80
25	**Du, Lillian** Supervisor: Richard Sultanian	CIM	A Comparison of Fecal Immunochemical Testing to Guaiac-Based Fecal Occult Blood Testing in a Colon Cancer Screening Program	81
26	**Dueck, Meghan** Supervisor: Paige Lacy	GS	NMR Metabolomics Analysis of Urine Samples and Correlation of Creatinine Levels with Jaffe Reaction Values	82
27	**Duraikannu, Arul** Supervisor: Douglas Zochodne	PDF	Manipulation of APC-β-Catenin signaling pathway promotes peripheral nerve regeneration	83
28	**Fiteih, Yahya** Supervisor: Harissios Vliagoftis	GS	Role of RIP2 in allergic airway inflammation	84
29	**Gurtu, Vikram** Supervisor: Evangelos Michelakis	SSR	Obesity From Leptin Receptor Deficiency Provides Resistance to the Development of Pulmonary Hypertension from Monocrotaline	85
30	**Hamza, Shereen** Supervisor: Branko Braam	PDF	NOVEL APPROACH FOR DIRECT ASSESSMENT OF IN VIVO RENAL SYMPATHETIC NERVE ACTIVITY IN RESPONSE TO ELEVATED RENAL VENOUS PRESSURE IN RATS	86

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
31	**Hassanzadeh Keshteli, Ammar** Supervisor: Karen Madsen / Leo Dielema	GS	Adherence to an Anti-Inflammatory Diet for 6 Months Can Decrease Fecal Calprotectin in Ulcerative Colitis Patients: Preliminary Findings of a Randomized Controlled Trial	87
32	**Heffernan, Courtney** Supervisor: Richard Long	GS	A Clinical Heuristic to Determine the Likelihood of Typical Adult-type Pulmonary Tuberculosis	89
33	**Henni, Amina Sarah** Supervisor: A. Russell	CIM	A Case of Scrotal Tophaceous Gout and Review of the Literature	91
34	**Highet, Megan** Supervisor: Karen Goodman	PDF	The Meaning of Symptoms: Illness Narratives as a Means for Describing Self-Perceived Impacts of H. pylori Infection among Residents of an Arctic Community	93
35	**Hnatiuk, Mark** Supervisor: Anthea Peters	SSR	Routine Serum Protein Electrophoresis Does Not Predict the Development of Post-Transplant Lymphoproliferative Disorder in Heart Transplant Patients: A Quality Improvement Project.	94
36	**Hong, Yongzhe** Supervisor: Sean McMurtry	GS	Administrative data are not sensitive for the detection of peripheral artery disease in the community	96
37	**Huang, Xiaohua** Supervisor: Branko Braam	GS	Acute Elevation of Renal Venous Pressure Increases Renal Vascular Resistance via Renal Nerves in Rats	98

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
38	**Ishaque, Abdullah** Supervisor: Sanjay Kalra	GS	Voxel-Wise Texture Analysis of Diffusion MRI Reveals Changes in Amyotrophic Lateral Sclerosis	99
39	**Jovanovic, Vojislav** Supervisor: Brendan Halloran	SSR	MICROARRAY ANALYSIS OF CROHN'S DISEASE AND CORRELATION WITH TRADITIONAL CLINICAL AND HISTOLOGIC FEATURES	101
40	**Kashur, Rabia** Supervisor: Robert Welsh	GS	CLINICAL RELEVANCE of The FIRST AVAILABLE 12 LEAD ECG IN PATIENTS WITH SYMPTOMS SUSPICIOUS FOR ACUTE CV DISEASE: Providing Rapid Out of Hospital Acute Cardiovascular Treatment-3 (PROACT-3) ECG SUBSTUDY	103
41	**Klostermann, Natalie** Supervisor: Karen Kroeker	GS	An individualized and multi-faceted transition intervention is needed for pediatric patients with inflammatory bowel disease	105
42	**Krishnan, Anand** Supervisor: Douglas Zochodne	PDF	Understanding how to salvage peripheral neurons: implications for regenerating nerves	107
43	**Kwong, Lorie** Supervisor: Sarah Chapelsky	CIM	Normalization of Pulmonary Function after Sleeve Gastrectomy in a Patient with Occupational Asthma	108
44	**Lalani, Aly-Khan** Supervisor: Naveen Basappa	SSR	Real world outcomes of patients with metastatic renal cell carcinoma (mRCC) using first-line sunitinib or pazopanib: the Canadian experience	109

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
45	**Lam, Anna** Supervisor: Peter Senior	SSR	Assessment of Islet Engraftment in Clinical Islet Transplantation Using BETA-2 Score	111
47	**Liu, Jonathan** Supervisor: Kieran Halloran	CIM	Baseline Lung Allograft Dysfunction Negatively Impacts Survival Following Lung Transplantation	113
48	**Lorenzana-Carrillo, Areli** Supervisor: Nadia Jahroudi	GS	Correlation between endothelial cell heterogeneity and expression of VWF in distinct organs.	115
49	**Luig, Thea** Supervisor: Denise Campbell-Scherer / Arya Sharma	PDF	Tackling the 'In-between' in the Implementation of Complex Interventions: the 5As Team Intervention to Improve Weight Management in Primary Care	116
50	**Mercer, Robert** Supervisor: David Westaway	PDF	A Novel Gerstmann-Sträussler-Scheinker Disease insertion mutation in the Prnp gene causes disease in transgenic mice.	117
51	**Mojiri, Anahita** Supervisor: Nadia Jahroudi	GS	Von Willebrand factor expression by cancer cells of non-endothelial origin and its functional consequences	118

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
52	**Mojiri, Anahita** Supervisor: Nadia Jahroudi	GS	Endothelial cells of distinct organs exhibit heterogeneity in response to hypoxia with regard to von Willebrand factor transcriptional regulation	119
53	**Nair, Sindhu** Supervisor: Paige Lacy	PDF	METABOLOMICS OF WELDING FUME EXPOSURE: A NOVEL BIOMARKER APPROACH FOR MONITORING HEALTH IN WELDER APPRENTICES	120
54	**Ney, Michael** Supervisor: Puneeta Tandon	CIM	Pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates: a systematic review	121
55	**Ng, Kurtis** Supervisor: Dean Befus	GS	Antiviral Response of Human Mast Cells and Airway Epithelial Cells to Influenza A Exposure	123
56	**Parajuli, Nirmal** Supervisor: Jason Dyck	PDF	The cardiac effects of deletion of adipocyte-specific ATGL.	124
57	**Park, Heekuk** Supervisor: Karen Madsen	PDF	Rifaximin in combination with a western-style diet induces ileal inflammation and enhances growth of Proteobacteria in IL-10-/- mice	125
58	**Patel, Arti** Supervisor: Jack Jhamandas	PDF	Intra-peritoneal administration of amylin receptor antagonist, cyclic AC253, in Aβ over-expressing (TgCRND8) mice	126

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
59	**Quach, Kimberly** Supervisor: Richard Long	GS	Clinical, Laboratory, and Treatment Outcome Characteristics of Foreign-Born Pulmonary Tuberculosis Patients in Alberta by Immigration Status, 2004-2013	127
60	**Radhakrishnan, Jeyasundar** Supervisor: Padma Kaul	PDF	Impact of physician characteristics on outcomes in patients with heart failure	128
61	**Rahbari, Mandana** Supervisor: Andrew Mason	GS	Virological Footprint of T-cell Responses in Patients with Primary Biliary Cirrhosis	130
62	**Rahimi, Behruz** Supervisor: Peter Senior	CIM	Biopsy Proven Insulitis of Clinical Islet Transplantation is not Reversed by Steroid Therapy	131
63	**Richard, Alby** Supervisor: Janis Miyasaki	SSR	Readability of Advance Directive Forms and Health Literacy in Canada: Missing the Mark	133
64	**Roberts, Janet** Supervisor: Stephanie Keeling / Steven Katz	CIM	Evaluation of Patient Satisfaction With the On-TRACC Program; Benefits of a 'Joint' Approach	135

Poster Presentations

Lower Level: John W. Scott Health Sciences Library
All Day Viewing

Poster #	Name		Title	Page
65	**Rueda-Clausen, Christian** Supervisor: Raj Padwal / Arya Sharma	CIM	Early programming of glucose metabolism among children with obesity born from complicated pregnancies	136
66	**Silva, Melissa** Supervisor: Leo Dieleman	GS	Comparison of Quantum Blue Rapid Test versus Fecal Calprotectin ELISA as a Non-invasive Marker to Predict Colonic Inflammation in Ulcerative Colitis	137
67	**Slomp, Flo** Supervisor: Bruce Dick	GS	Extrapolation of sensory data into a pain score	138
68	**Soudy, Rania** Supervisor: Jack Jhamandas	PDF	IDENTIFICATION OF SHORT BRAIN PENETRANT AMYLIN RECEPTOR BASED PEPTIDES AS NOVEL THERAPEUTICS FOR ALZHEIMER'S DISEASE	139
69	**Zahran, Somaya** Supervisor: Peter Hwang	GS	Distinguishing cardiac Troponin fragment sizes in patients with type 1 vs type 2 myocardial infarction	140
70	**Zervopoulos, Sotirios** Supervisor: Evangelos Michelakis	GS	Microtubule acetylation facilitates intracellular communication: a new mitochondria-to-nucleus "highway"	141
71	**Zheng, Yufei** Supervisor: Philip Jacobs	GS	Does a transition service reduce ALC days and total non-acute-care days for stroke patients in Alberta?	142

Scoring Criteria

Oral & Poster Prsentations
(1=Poor, 5= Excellent)

Clarity and Justification of the Research Questions/Hypothesis	1 2 3 4 5
Appropriateness of the Methods Used to Answer the Questions/Hypothesis	1 2 3 4 5
Validity and Relevance of the Results to the Questions/Hypothesis	1 2 3 4 5
Quality of the Discussion and Conclusion	1 2 3 4 5
Visual Layout and Visual Impact	1 2 3 4 5
Oral Response to Adjudicator's Question	1 2 3 4 5
TOTAL SCORE	**_____ 35**

Mild Therapeutic Hypobaria Improves Left Ventricular Function after Acute Myocardial Infarction in Mice

Shahid, Anmol., McMurtry, S.M.
Supervisor: Sean Michael McMurtry

INTRODUCTION

Humans living at higher elevations have lower risk for myocardial infarction (MI) and better post-MI survival. We have shown that acute reductions in atmospheric pressure enhance arterial vasodilation in an endothelium-independent manner ex vivo and reduce afterload in vivo in mice. We hypothesized that afterload reduction induced by mild therapeutic hypobaria after acute MI would improve myocardial function.

METHODS

Left-anterior descending artery (LAD) ligation was performed on three-month old C57BL6 males. Group A mice (control, n=9) were allowed to recover from the surgery at atmospheric pressure (754 mmHg). Group B mice (n=8) were placed in a hypobaric chamber to recover from the LAD ligation for 3-hours at 714 mmHg, a pressure chosen to mimic an elevation of 1500 m and avoid hypoxemia. The successful induction of anterior MI was confirmed by echocardiography 24 hours after the surgery. Group B mice were administered 3-hours of hypobaric treatment daily for 7 days. Echocardiographic evaluation of left ventricular (LV) function was performed for all mice on Day 8.

RESULTS

Echocardiography confirmed large anterior MI's in both groups with no difference in ejection fraction (EF) or cardiac output at day 1. After 7 days of therapeutic hypobaria, there was a 14.2±5.3% improvement in EF for Group B mice ($p<0.01$ versus Day 1), and no change for Group A mice. Similarly, cardiac output and stroke volume increased by 11.48±3.9 mL/min and 24.33±8.3 µL, respectively, in Group B mice ($p<0.01$ versus Day 1) after 7 days of hypobaric treatment while Group A mice showed no significant improvement.

CONCLUSIONS

We conclude that acute afterload reduction achieved by mild therapeutic hypobaria improves myocardial function after acute MI in mice. This finding may have translational potential as a novel therapy for acute MI in humans.

Supervisor: Dr. Sean Michael McMurtry

Back to Previous Page

Early initiation of anti-TNF therapy is cost-saving compared to late initiation for patients with Crohn's disease

Candace L. Beilman (1), Christopher Ma (1), Christopher McCabe (2), Richard N. Fedorak (1) , Brendan Halloran (1)
Supervisor: Dr. Brendan Halloran

INTRODUCTION

Anti-TNF therapies are effective for the induction and maintenance of remission for patients with Crohn’s disease (CD), and are generally prescribed once patients have failed to respond to conventional, less-costly medical therapies. Early initiation (within two years of diagnosis) of anti-TNF reduces the rate of surgery and loss of response by minimizing chronic, irreversible changes to the bowel. However, the costly nature of these medications gives rise to concerns regarding early usage. The aim of this study was to determine if early or late initiation of anti-TNF therapy is most cost-effective for the management of CD.

METHODS

A Markov model was constructed that simulates the progression of patients with CD after the initiation of either infliximab or adalimumab. Using this model, we compared the lifetime cost-effectiveness of early initiation versus late initiation of anti-TNF therapy using published loss of response rates. Transition probabilities were determined through a literature search and costs were obtained from the CIHI Patient Cost Estimator. Utility scores were obtained from published literature using the Standard Gamble approach. Probabilistic sensitivity analysis was used to characterize uncertainty related to outcomes.

RESULTS

Over a patient’s lifetime, early initiation of infliximab yielded an additional 0.74 quality-adjusted life years (QALYs) and saved $49,755 compared to late initiation of infliximab. Early initiation of adalimumab yielded an additional 0.92 QALYs and saved $52,610 compared to late initiation. At a willingness-to-pay threshold of $50,000, early initiation of infliximab had a 66% chance of being cost-effective compared to late initiation. Similarly, early initiation of adalimumab had a 68% chance of being cost-effective compared to late initiation of adalimumab.

CONCLUSIONS

Based on our current model, early initiation of both infliximab and adalimumab appears to dominate late initiation for patients with CD and may serve to support early treatment with anti-TNF therapy from both a cost and patient outcome perspective.

Supervisor: Dr. Brendan Halloran

Back to Previous Page

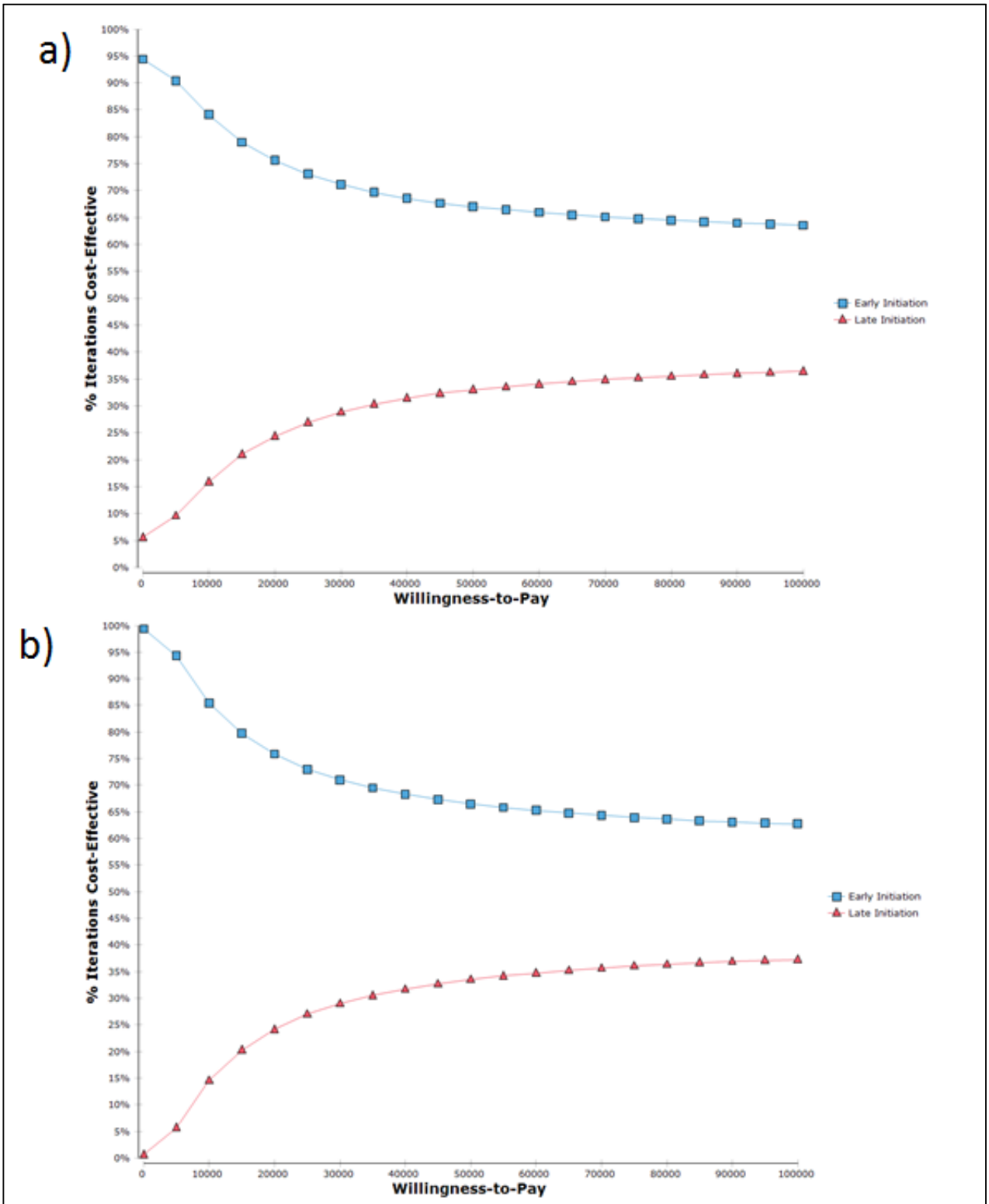


Figure 1. Cost-effectiveness acceptability curves for early versus late initiation of a) infliximab and b) adalimumab.

c-Myc 1 is reversibly induced by suppression of mitochondrial function

BOUKOURIS A, KINNAIRD A, PAULIN R, ZERVOPOULOS S, GURTU V, SUTENDRA G, MICHELAKIS ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

c-Myc is a transcription factor important for mitochondrial function. c-Myc 2, the predominant isoform, is well-studied in cancer, where its upregulation drives proliferation and apoptosis-resistance. The much less-studied c-Myc 1 isoform is thought to inhibit proliferation and be induced under decreased nutrient availability. We hypothesized that c-Myc 1 may be induced by primary mitochondrial suppression (mimicking nutrient unavailability) and that under metabolic stress, the c-Myc 1/c-Myc 2 ratio may determine cell fate (proliferation, death).

METHODS

We exposed A549 lung cancer cells to well-known inhibitors of mitochondrial function: Ethidium Bromide (EtBr; depletes mitochondrial DNA), Oligomycin (ATP synthase inhibitor), hypoxia or siRNA against sirtuin-3 (the main mitochondrial deacetylase, the absence of which globally suppresses mitochondrial function). We studied c-Myc and cleaved Caspase-3 expression (immunoblots), mitochondrial respiration (Seahorse Analyzer) and cell proliferation (Ki-67 expression).

RESULTS

c-Myc 1 was absent in non-cancer cells (small airway epithelial; proximal tubule), but was expressed in their related cancer lines (A549 lung cancer and 786-O renal cancer cells). A further robust induction of c-Myc 1, at the expense of c-Myc 2, was observed in A549 cells treated with all of the tested mitochondrial inhibitors, which significantly decreased mitochondrial respiration. Removal of these mitochondrial inhibitors restored mitochondrial function and normalized the c-Myc 1/c-Myc 2 ratio in the same cells. This reversible induction of c-Myc 1 in EtBr-treated A549 cells correlated with decreased mitochondrial DNA levels, decreased respiration, decreased proliferation (37.1 vs. 59% positive cells for the proliferation marker Ki-67) and decreased apoptosis (decreased cleaved Caspase-3 levels).

CONCLUSIONS

c-Myc 1 is reversibly induced by suppression of mitochondrial function. Mitochondrial suppression is found in many diseases (e.g. cancer, pulmonary hypertension, pulmonary fibrosis) or important biological states (e.g. senescence, stemness, hibernation). Thus, the discovery of c-Myc 1 induction, antagonizing the well-studied c-Myc 2, may have important implications for drug development in cancer and beyond.

Supervisor: Dr. Evangelos Michelakis

Back to Previous Page

I4855M is a novel RyR2 suppression-of-function mutation underlying an overlapping phenotype of Wolff-Parkinson-White Syndrome, Left Ventricular Non-compaction Cardiomyopathy, Catecholaminergic Polymorphic Ventricular Tachycardia and Sudden Cardiac Arrest

Thomas M. Roston (1,2), Shubhayan Sanatani (2), Andrew D. Krahn (2), Julie Hathaway (2), Filip van Petegem (2), Ruiwu Wang (3), Wenting Guo (3), S.R. Wayne Chen (3), Anna Lehman (2)
Supervisor: Dr. Shubhayan Sanatani

INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an ion channelopathy usually caused by gain-of-function mutations in the Ryanodine Receptor-2 (RyR2) gene. Left ventricular non-compaction (LVNC) is an unusual cardiomyopathy. An LVNC-CPVT overlap syndrome may exist in rare cases of exon 3 deletion in RyR2.

METHODS

Clinical and genetic assessment of the proband and family were conducted. We created a homology model of the RyR2 pore-region to determine variant localization. The I4855M variant was functionally characterized by using caffeine-induced calcium release in HEK293 cells and [3H]ryanodine binding assays.

RESULTS

An asymptomatic 10 year-old female proband underwent cardiac screening before starting psychostimulants for attention deficit disorder. Family history of sudden death was strong, including autopsy-negative sudden death in her maternal grandmother at 51 years of age. The proband’s ECG showed pre-excitation that abruptly abated early in exercise. Her echocardiogram demonstrated LVNC. While her mother was undergoing family screening for cardiomyopathy, the girl survived a cardiac arrest. Genetic testing revealed a RyR2 variant (I4855M). Her mother had a normal ECG, ventricular arrhythmia on exercise, LVNC on echocardiography and carried the I4855M variant. Our homology model of the RyR2 pore-region showed that the I4855M variant is in the 'inner vestibule', a water-filled cavity where ions can remain in a hydrated fashion. I4855M appeared to interfere with calcium permeation, and may also affect interactions between the four RyR2 pore subunits. I4855 is highly conserved, predicted in silico to be damaging, and leads to suppression of caffeine-induced calcium release in HEK293 cells and [3H]ryanodine binding to the channel. Co-expression of the mutant with wildtype RyR2 indicated a dominant negative effect of I4855M on the wildtype channel.

CONCLUSIONS

A novel variant in the C-terminus of RyR2 underlies an overlapping phenotype of CPVT, LVNC and Wolff-Parkinson-White syndrome. Expression and functional studies in HEK293 cells suggest that I4855M is actually a suppression-of-function mutation

Back to Previous Page

Metabolic Modulation as a Novel Therapy in Chemotherapy Induced Cardiotoxicity

Bruno Saleme, Adam Kinnaird, Aristeidis Boukouris, Sotirios Zervopolous, Vikram Gurtu and Gopinath Sutendra
Supervisor: Dr. Gopinath Sutendra

INTRODUCTION

Chemotherapy Induced Cardiotoxicity (CIC) is a serious complication that results in early termination of cancer therapies, despite responsive tumors. There are no therapies to prevent CIC, as our understanding of the mechanisms in this condition is limited. Intriguingly, similar metabolic processes (increased glycolysis) has been described in heart failure and cancer, suggesting metabolic therapies may be beneficial against both diseases. One challenge in designing CIC therapies is protecting the heart against apoptosis without hindering chemotherapy-mediated tumor apoptosis. An intriguing difference between the myocardial and tumor microenvironments is the former is normoxic (oxidized) and the latter hypoxic (reduced), suggesting that targeting metabolic redox-sensitive proteins induced by chemotherapy agents in the heart may provide selectivity against CIC, without compromising tumor suppression. We hypothesized that cardiotoxic agents induce the inactive form of the metabolic redox-sensitive protein pyruvate kinase-M2 (PKM2) in the heart and therapeutic activation may prevent CIC.

METHODS

Cell lines: H9c2, A549; Reagents: Adriamycin, TEPP-46, H_2O_2, Diamide, DTT; Techniques: immunoblots and confocal (apoptosis: caspase-3/TUNEL/Bax/p21); in-vivo: xenotransplanted mice with tumors were randomized/treated for 14 days with vehicle, TEPP-46, Adriamycin or Adriamycin+TEPP-46.

RESULTS

The cardiotoxic agent Adriamycin induced the inactive form of PKM2 in H9c2 cardiomyocytes in both normoxia and hypoxia. Adriamycin-mediated apoptosis in H9c2 was inhibited by the PKM2 activator TEPP-46 in an oxidized (normoxia, H_2O_2, diamide), but not reduced (hypoxia, DTT) environment, and additionally increased apoptosis in A549 (pseudohypoxic) cancer cells. Furthermore, activation of oxidized, but not reduced PKM2 by TEPP-46 resulted in inhibition of the pro-apoptotic transcription factor p53. In-vivo, Adriamycin induced the inactive form of PKM2 and increased apoptosis in the myocardium, and this was inhibited by TEPP-46, which further decreased lung tumor size in xenotransplanted mice

CONCLUSIONS

Our novel data provide the first evidence that redox-targeted metabolic therapies are beneficial against CIC, while synergistically decreasing tumor growth.

Supervisor: Dr. Gopinath Sutendra

Back to Previous Page

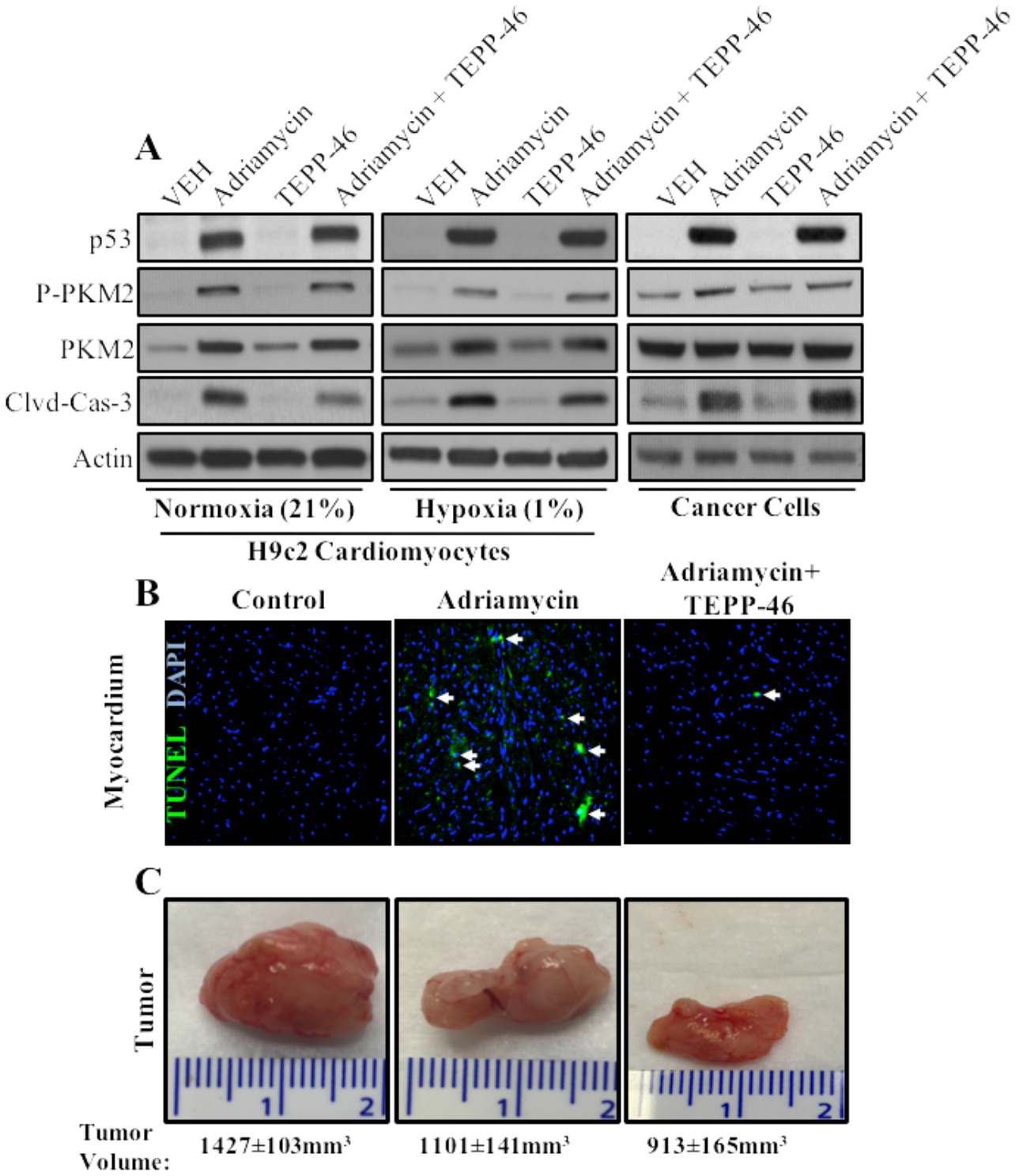


Figure. PKM2 Activators As A Novel Therapy In Chemotherapy-Induced Cardiotoxicity

(A) The PKM2 activator TEPP-46 inhibits Adriamycin-mediated apoptosis (as assessed by cleaved caspase-3) in H9c2 cardiomyocytes in normoxia (i.e. oxidized), but not hypoxia (i.e. reduced). TEPP-46 enhances Adriamycin-mediated apoptosis in A549 cancer cells (i.e. reduced). Actin was used as a loading control.

(B) TEPP-46 treatment partially prevents Adriamycin-induced apoptosis (TUNEL in green) in the myocardium (MHC+ cells; not shown) of xenotransplant mice with human tumors, protecting against decreased cardiac function.

(C) TEPP-46 enhances Adriamycin-mediated tumor suppression assessed by tumor volume and size.

Back to Previous Page

THE VON HIPPEL LINDAU (VHL) TUMOR SUPPRESSOR INHIBITS P21 TO PROMOTE PROLIFERATION AND APOPTOSIS-RESISTANCE IN CANCER

Adam Kinnaird, Aristeidis Boukouris, Vikram Gurtu, Bruno Saleme, Sotirios Zervopoulos, Gopinath Sutendra, and Evangelos D. Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

VHL is considered a tumor suppressor since it degrades the pro-angiogenic, pro-proliferative Hypoxia-Inducible Factor (HIF). Its functional loss is associated with vascular tumors, like renal cell carcinoma (RCC). A HIF-independent mechanism by which VHL unexpectedly promotes proliferation was described recently but its basis remains unknown. VHL functions like an adaptor for the components of HIF's degradation machinery and this may apply to non-HIF proteins. We hypothesized that VHL directly binds and degrades the cyclin-dependent kinase inhibitor p21, increasing proliferation and apoptosis-resistance. This may be a novel means of p21inhibition, which is thought to mainly be regulated transcriptionally by p53.

METHODS

VHL-deficient RCC cells (expressing HIF2a but not HIF1a) were transiently (adenoviral) or stably (lentiviral) transduced with VHL. Co-immunoprecipitations, immunoblots, confocal imaging and siRNA transfections were performed using standard techniques.

RESULTS

Transient and sustained wild-type VHL expression (but not mutant VHL lacking the adaptor domain) robustly decreased p21 protein levels. VHL-deficient RCC cells, lacking HIF (HIF2a siRNA) had unaltered p21 levels. VHL over-expressing cells, also expressing HIF (induced by hypoxia or the AdCA5 virus carrying non-degradable HIF1a) exhibited low p21 levels compared to VHL-deficient cells. VHL over-expression increased cell number and PCNA, and reduced apoptosis (cleaved-caspase-3). Induction of p21 and apoptosis by doxorubicin was significantly attenuated in RCC over-expressing VHL vs VHL-deficient cells. Treatment of VHL-expressing cells with MG-132 (proteasome inhibitor) restored p21 to the level of VHL-deficient cells. VHL co-immunoprecipitated with p21 in the presence of MG-132.

CONCLUSIONS

These results suggest a physical-interaction between VHL and p21 where VHL degrades p21 via the proteasome machinery. This previously unidentified mechanism suggests that in conditions where anti-proliferative effects on HIF may be opposed by pro-proliferative effects on p21, VHL may paradoxically promote cancer. Chemotherapies like doxorubicin that cause a p53-driven induction of p21 may be ineffective in VHL-rich tumors, opening a novel precision medicine approach.

Back to Previous Page

NK Cell CD16α IgG Fc Receptors Are Activated in Antibody-Mediated Renal Allograft Rejection

MD Parkes(1), PF Halloran(1), LG Hidalgo(2)
Supervisor: Dr. Philip Halloran

INTRODUCTION

INTRODUCTION: Antibody-mediated rejection (ABMR) is a microvascular disease driven by cellular responses to donor-specific antibodies (DSA) bound to graft endothelium, and is the leading cause of renal allograft failure. In ABMR, CD16α is thought to activate NK cells in response to DSA, but this has not been shown. CD16α-mediated NK activation shares mechanisms with effector T cell receptor (TCR) stimulation; we hypothesized that CD16α-inducible NK transcripts are associated with ABMR vs. disease states without T cell-mediated pathology.

METHODS

METHODS: We cultured primary human NK cells and CD8+ T cells +/- CD16α or CD3 stimulation, respectively, and assessed gene expression changes using microarrays. We identified the top CD16α-inducible NK transcripts, focused on the 11 expressed >1000 in stimulated NKs (Fig 1A), and examined them in 703 biopsies.

RESULTS

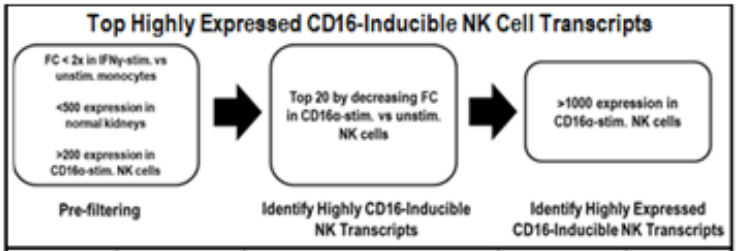
RESULTS: The 7 CD16-inducible NK transcripts associated with ABMR ($p<10^{-7}$) are depicted in Fig. 2. These include CD160 and XCL1, which were increased in NK cells and CD8+ T cells, and associated with both ABMR and T cell-mediated rejection (TCMR) (Fig 1B). Membrane protein CRTAM promotes IFNG release and cytotoxicity in NK cells and CD8+ effector T cells; chemokines CCL4 and CCL3, Fc-receptor-like protein FCRL3, and TNFRSF9 reflect shared functions between NK in ABMR and CD8+ T cells in TCMR.

CONCLUSIONS

CONCLUSIONS: Several CD16α-inducible transcripts are associated with ABMR. Many of these are also expressed in TCMR because CD16α and TCR engage overlapping signalling systems. CD160 and XCL1 are selective for CD16α-stimulated NK cells in pure ABMR with low TCMR molecular classifier scores, supporting the hypothesis that in ABMR the Fc portions of endothelium-bound DSA trigger NK CD16α, which has the potential to release cytokines and activate cytotoxicity. Weak ABMR associations of some CD16α-inducible transcripts may reflect additional expression in other cell types and disease states.

Supervisor: Dr. Philip Halloran

A



B

Gene	- $\log_{10}$(p value) ABMR vs EE -TCMR, -Mixed	Fold Chg NK Stim vs Unstim	Expression NK Stim	- $\log_{10}$(p value) TCMR vs EE -Mixed	Fold Chg CD8+ T Stim vs Unstim
CCL4	**24.10**	43.4	12522	19.28	83.5
CD160	**18.79**	9.6	4602	6.50	9.5
CCL3	**14.96**	23.1	7433	18.35	18.2
XCL1	**13.71**	14.4	1344	21.83	242.9
CRTAM	**10.16**	164.7	7361	26.08	7.5
FCRL3	**9.89**	9.3	2568	19.99	2.8
TNFRSF9	**7.87**	90.1	3835	25.78	37.1
FEZ1	4.55	22.0	2624	1.05	5.1
NR4A2	4.39	13.4	1888	4.75	8.8
IFNG	3.76	110.0	6484	40.32	259.2
IRF4	1.59	11.2	1749	9.20	18.8

Figure 1. (A) Identification of highly expressed CD16-inducible NK transcripts. **(B)** Outputs from (A), sorted by decreasing association with ABMR vs everything else except TCMR and mixed rejection ("ABMR vs EE -TCMR -Mixed"). TCMR comparison is against everything else except mixed rejection ("TCMR vs EE -Mixed"). *Underlined:* highly expressed CD16-inducible transcripts with $p < 10^{-7}$ in ABMR vs everything else except TCMR and mixed rejection.

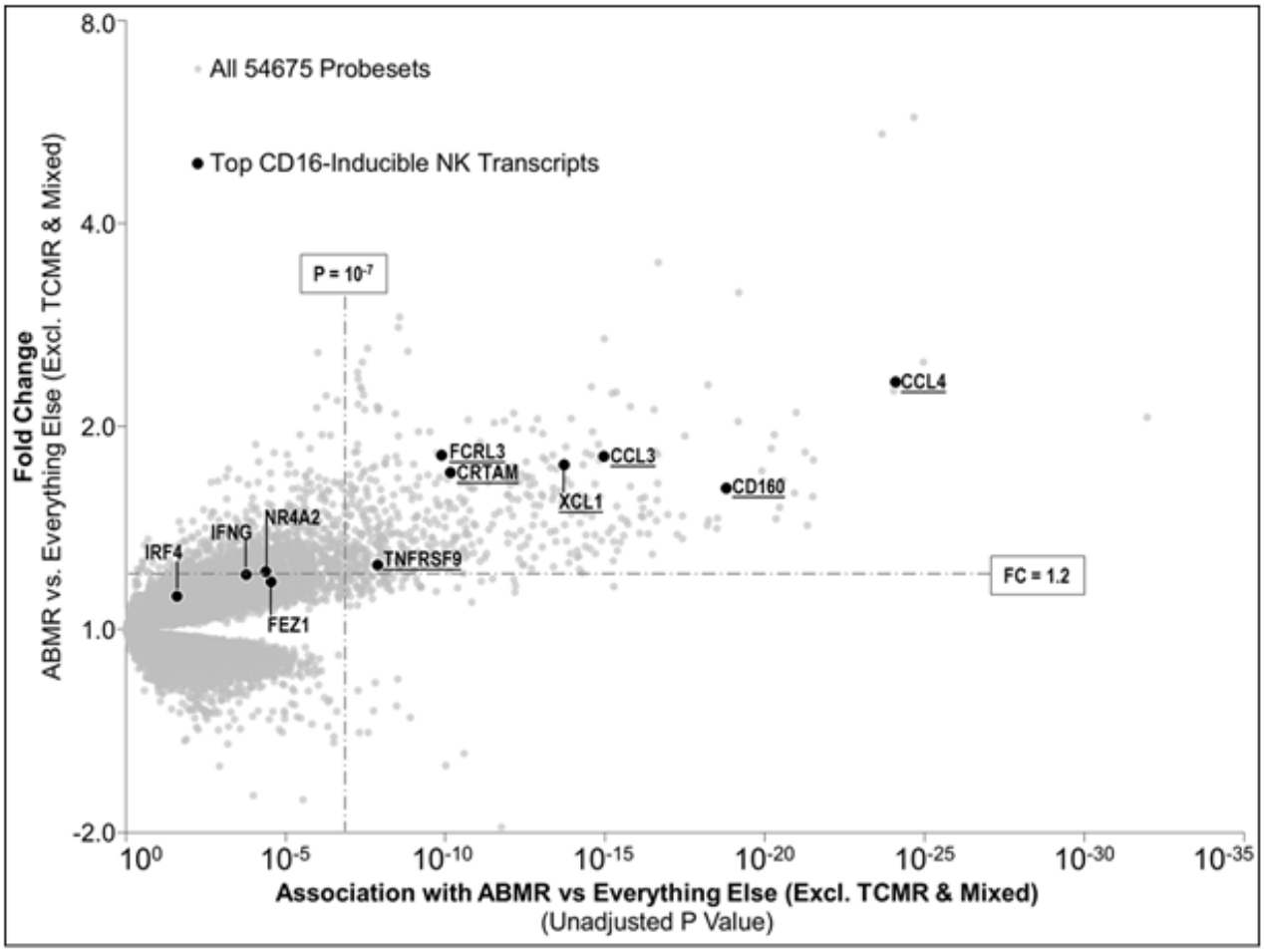


Figure 2. Volcano plot highlighting the top CD16-inducible NK transcripts with >1000 expression in stimulated NK cells, plotted by fold change and association with ABMR vs everything else except TCMR and mixed rejection. **Underlined:** Top CD16 inducible NK transcripts with $p < 10^{-7}$ in ABMR vs everything else except TCMR and mixed rejection.

Back to Previous Page

Insulin Treatment Prevents Neuroinflammation and Neuronal Injury with restored Neurobehavioral Function in Models of HIV/AIDS Neurodegeneration

Manmeet K Mamik, Eugene L. Asahchop, Yu Zhu, William G. Branton, Brienne A. McKenzie, Christopher Power
Supervisor: Dr. Christopher Power

INTRODUCTION

HIV-1 infection of the brain causes neuroinflammation and contributes to the development of the neurodegenerative syndrome, HIV-associated neurocognitive disorder (HAND) for which there is no specific treatment. We investigated the actions of insulin in ex vivo and in vivo models of HAND, since insulin signaling has been implicated in HIV infection.

METHODS

Primary human neural cell cultures and Feline Immunodeficiency Virus (FIV) animal model were used in the study. Cell cultures were infected with HIV followed by treatment with insulin (0.1-1 IU/ml). Animals were infected with FIV, followed by intranasal (IN) administration of insulin. Neurobehavioral tests were performed and brains analyzed for inflammatory gene expression.

RESULTS

Increased neuroinflammatory gene expression was observed in brains of HIV-infected patients. The insulin receptor was detected on both neurons and glia but its expression was unaffected by HIV-1 infection. Insulin treatment of HIV-infected primary human fetal microglia (HFM) suppressed supernatant HIV-1 p24 levels, reduced CXCL10 and IL-6 transcript levels while PPAR-γ expression was induced. Feline immunodeficiency virus infected (FIV[+]) cats, treated with IN insulin (daily 20.0 IU/200 µl for 6 weeks) or vehicle (PBS), revealed that IN insulin treatment reduced brain CXCL10 and IL-6 expression in FIV[+] animals together with suppressed FIV detection although PPAR-γ in glia was increased by insulin treatment, compared to PBS-treated FIV[+] animals. These molecular changes were accompanied by reduced glial activation in cerebral cortex and white matter of insulin-treated FIV[+] animals. Neuronal counts in parietal cortex, striatum and hippocampus were higher in the FIV[+]/Insulin group compared to the FIV[+]/PBS group. Moreover, IN insulin treatment improved neurological performance including both memory and motor functions in FIV[+] animals.

CONCLUSIONS

Insulin exerted ex vivo and in vivo antiviral, anti-inflammatory and neuroprotective effects in models of HAND, representing a new therapeutic option for patients with inflammatory or infectious neurodegenerative disorders including HAND.

Supervisor: Dr. Christopher Power

Back to Previous Page

INSULIN REGULATES PROTEINASE-ACTIVATED RECEPTOR-2 EXPRESSION ON AIRWAY EPITHELIUM

Vivek Gandhi and Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Activation of Proteinase-Activated Receptor-2(PAR-2), a receptor for aeroallergens and endogenous serine proteinases, mediates allergic sensitization and airway inflammation in animal models of asthma. PAR-2 expression is increased on airway epithelium of asthmatic individuals, but factors responsible as well as the consequences of increased PAR-2 expression are unknown. We hypothesize that cellular stress, a characteristic of inflamed airways diseases, regulates PAR-2 expression on airway epithelium.

METHODS

The growth factors we added to Normal Human Bronchial Epithelial (NHBE) cell culture media are bovine pituitary extract, epidermal growth factor and insulin. Cells were cultured with or without growth factors (growth factor deprivation), or in the absence of individual growth factor for up to 48h. PAR-2 mRNA levels were studied by qRT-PCR. PAR-2 function was studied by measuring PAR-2-mediated calcium release from intracellular stores using a fluorescence-based assay.

RESULTS

We have shown that growth factor deprivation, but not oxidative stress or hypoxia, upregulates PAR-2 mRNA and protein expression in NHBE cells. By excluding individual growth factors we now show that growth factor deprivation-induced PAR-2 upregulation was the result of exclusion of insulin (insulin deprivation). Insulin deprivation for 24h and 48h increased PAR-2 mRNA levels by 1.7+/-0.1 fold (n=9) and 2.3+/- 0.3 fold (n=4), respectively. Addition of insulin reversed PAR-2 upregulation in insulin-deprived cells, but also in growth factor deprived cells. Insulin deprived cells showed increased intracellular calcium release upon PAR-2 activation compared to cells grown in the presence of insulin, indicating that the increased PAR-2 expression leads to increased PAR-2 function. Insulin deprivation also increased PAR-2 promoter activity, indicating that insulin deprivation-mediated upregulation in PAR-2 mRNA is due to increased PAR-2 gene transcription. Our preliminary results suggest that insulin deprivation-mediated PAR-2 upregulation is extracellular-signal-regulated kinase 1/2 (ERK1/2) dependent.

CONCLUSIONS

Understanding PAR-2 regulation in airway epithelial cells may lead to novel treatments for inflammatory diseases such as asthma.

Supervisor: Dr. Harissios Vliagoftis

Back to Previous Page

Community-Driven Research on Environmental Determinants of Gastritis Severity: Using Fish Intake as a Proxy for Mercury Exposure in Canadian Arctic Communities

E.V. Walker, S. Girgis, K.J. Goodman, The CANHelp Working Group
Supervisor: Dr. Karen Goodman

INTRODUCTION

Gastritis is characterized by inflammation of the gastric mucosa, induced by H.pylori infection or chemical irritants; chronic gastritis is theorized to initiate gastric carcinogenesis. Gastritis severity falls on a spectrum, with greater severity corresponding to greater mucosal injury. Causes of gastritis severity are not well known. Community-driven projects conducted by the CANHelp Working Group in the Canadian Arctic reveal a higher-than-expected prevalence of severe gastritis among H.pylori-positive (HP+) participants. Community input highlighted concern about the environmental contaminant mercury affecting digestive health. We present preliminary analysis of the effect of dietary exposure to mercury on severe gastritis prevalence among HP+ residents of Arctic Canada.

METHODS

We used fish consumption as a proxy for mercury exposure because eating contaminated fish is a major exposure pathway. Mercury concentration increases with fish size, so we used fish size to indicate dose. We collected data on diet and covariates from structured interviews. We offered upper endoscopy with gastric biopsy in Aklavik (2008) and Fort McPherson (2012), Northwest Territories and Old Crow (2011) Yukon. A pathologist graded gastritis as none, mild, moderate or severe. Logistic regression estimated ORs(95%CIs) for the effect of fish consumption on severe gastritis prevalence, adjusting for other dietary factors, age, sex, ethnicity, NSAIDs, alcohol, smoking and community of residence.

RESULTS

Among 161 HP+ people with complete data, severe gastritis prevalence was 45%. The odds of severe gastritis increased with fish consumption (OR=3.1(1.1,8.9) for consuming ≥3v.<1 servings/week) The OR for consuming large fish (average length ≥60cm) v. not was 3.6(1.0,13).

CONCLUSIONS

This preliminary analysis shows servings per week and size of fish consumed to be positively associated with gastritis severity in Arctic Canada. Further analysis will include estimates of the degree of mercury concentration in consumed fish.

Supervisor: Dr. Karen Goodman

Back to Previous Page

Incidence of Catheter-related Thrombosis in Acute Leukemia patients: a comparative, retrospective study of the safety of Peripherally-Inserted vs. Centrally-Inserted Central Venous Catheters.

Mohammad Refaei, M.D.1 Bruna Fernandes, R.N.2 Arun Pokhrel, Ph.D. 3 Marilyn Dawn Goodyear M.D. 4 Joseph Brandwein M.D.5 Cynthia Wu. M.D. 5*
Supervisor: Dr. Cynthia Wu

INTRODUCTION
Central venous catheters are a leading cause of upper extremity deep vein thrombosis. Concomitant severe thrombocytopenia makes anticoagulation for catheter-related thrombosis (CRT) in patients with acute leukemia (AL) a challenge. Incidence of CRT has been reported to be increased in those with peripherally-inserted central catheters (PICC) vs. those with centrally inserted ones (CICC).

METHODS
Our objective is to compare the incidence rate of CRT in leukemia inpatients who received either a PICC vs. CICC. We retrospectively reviewed 2 cohorts of adult inpatients admitted to Hematology with a new diagnosis of AL and who received either a PICC or a CICC. Baseline patient and catheter characteristics were recorded. Our primary outcome was the incidence rate of CRT in each group. The secondary outcomes included rates of infectious and mechanical complications.

RESULTS
633 patients received at least one CICC (325) or PICC (338) insertion. A total of 1331 insertions were recorded, with 41 (6.5%) and 82 (11.7%) CRT in the CICC and PICC groups, respectively. The cumulative incidence rates were 0.52 and 1.89 per 1000 catheter day in the CICC and PICC groups, respectively. Catheter type was the only significant risk factor for CRT (HR 2.9, p-value <0.0001).

CONCLUSIONS
The prevalence and incidence rates of CRT in our AL patients were higher than predicted for a general cancer patient population. These rates were higher in the PICC group compared to the CICC group. We recommend all AL inpatients receive a CICC over a PICC.

Supervisor: Dr. Cynthia Wu

Back to Previous Page

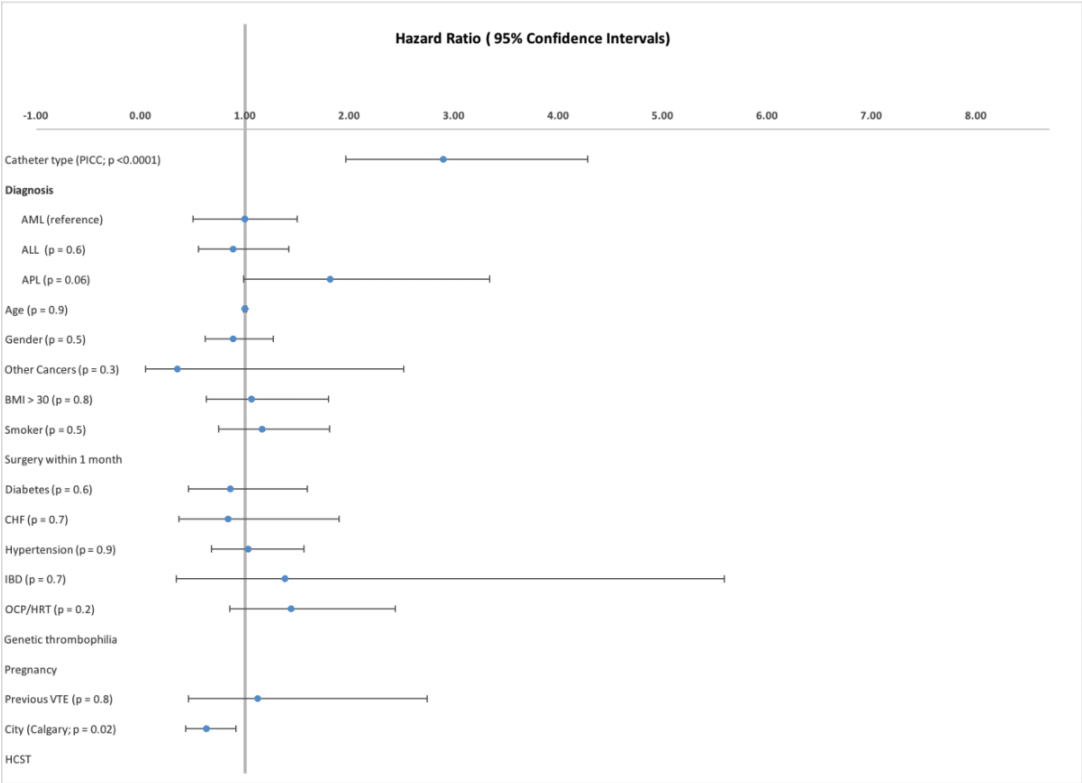


Figure 2: Univariate Cox Regression Analysis of Factors Affecting Catheter-related Thrombosis. Certain variables (e.g. Surgery within 1 month of CRT, genetic thrombophilia, pregnancy, and HSCT) did not have enough data to be analyzed in the cox model. AML (acute myeloid leukemia), ALL (acute lymphoblastic leukemia), APL (acute promeolocytic leukemia), BMI (body mass index), CHF (congestive heart failure), IBD (inflammatory bowel disease), OCP/HRT (oral contraceptive pill/hormonal replacement therapy), VTE (venous thromboembolism), HCST (hematopoietic stem cell transplant).

Table 6: Significant Factors in Cox Regression Multivariate Analysis Affecting All Secondary Outcomes (N=1331)

Outcome	Variable	HR (95% CI)	p-value
Recurrent CRT	IBD	10.6 (1.3-86.1)	0.03
	OCP/HRT	4.0 (1.0-15.7)	0.04
Concurrent VTE	BMI > 30	2.8 (1.3-5.9)	0.007
	Previous VTE	3.5 (1.2-10.0)	0.02
Catheter-related bacteremia	HCST	15.1 (8.3-27.8)	<0.0001
All-cause bacteremia	Diabetes	1.5 (1.0-2.3)	0.04
	HCST	8.8 (6.4-12.0)	<0.0001
Mechanical complications	Catheter type (PICC)	2.3 (1.5-3.7)	<0.0001

CRT (catheter-related thrombosis), VTE (venous thromboembolism), BMI (body mass index), IBD (inflammatory bowel disease), OCP/HRT (oral contraceptive pill/hormonal replacement therapy), HCST (hematopoietic stem cell transplant).

Back to Previous Page

Efficacy of hepatitis B counseling and vaccination in patients with inflammatory bowel disease receiving anti-TNF therapy

ThucNhi Tran Dang, Cathy Lu, Rowan Lumb, Spencer Krahn, Karen Kroeker, and Richard Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Immunosuppressive therapies are the cornerstone of inflammatory bowel disease (IBD) treatment but increase risk of infections. Routine hepatitis B (HB) virus screening and vaccination is recommended in all IBD patients prior to initiation of anti-TNF therapy by the European Crohn's and Colitis Organization (ECCO) guidelines published in 2009. Recent studies suggest less than optimal screening for HB in IBD patients.

Our objectives were:
1) Determine the proportion of IBD patients receiving anti-TNF therapy who have been screened and vaccinated against HB
2) Measure the immune response to HB vaccinations for non-immune patients receiving anti-TNF therapy

METHODS

Patients receiving anti-TNF were enrolled in this retrospective cohort study. Demographics, IBD characteristics, HB history, and immunosuppressive treatment history were obtained through a survey and chart review. HB serology was obtained to determine vaccination status (HBs-Ab > 10U/L was defined as immune). Non-immune patients were contacted for HB vaccinations. HB serology was re-measured at 3 months post-vaccination to determine response to vaccination.

RESULTS

To date, 245 patients on anti-TNF therapy have been enrolled. Only 1% report HB counseling and 3% report vaccinations prior to initiation of anti-TNF. Patients screened prior to initiation of anti-TNF improved pre-2010 vs. post-2010 from 9% to 58% ($p < 0.001$). Similarly, number of patients who were HB-immune improved from 16% pre-2010 to 38% post-2010 ($p < 0.002$). There was no difference in IBD diagnosis or gender pre- and post-2010, but patients screened or vaccinated post-2010 were younger (36.3 vs. 42.5, $p = 0.005$).

CONCLUSIONS

There is a lack of counseling perceived by patients regarding HBV vaccinations. Although rates of HB screening and vaccination anti-TNF is improving, there remains a considerable number patients whose HBV status remains unknown. The second phase of our study will investigate the immune response of IBD patients receiving anti-TNF to the standard HBV vaccinations.

Supervisor: Dr. Richard Fedorak

Back to Previous Page

Back to Previous Page

Sleep quality, and factors influencing it, in the general medicine inpatient population

Selina Dobing, Natalia Frolova, Finlay A. McAlister, Jennifer S. Ringrose
Supervisor: Dr. Jennifer Ringrose

INTRODUCTION

Sleep quality in hospitalized patients is not well characterized. Our goals were to characterize hospital sleep quality and identify potentially modifiable barriers to good sleep in the adult general internal medicine (GIM) population.

METHODS

GIM inpatients at a quaternary centre in Edmonton, Canada completed a survey, including the Verran-Snyder Halpern (VSH) questionnaire, to characterize the previous night's sleep within 48 hours prior to discharge. A chart review was also completed to assess comorbidities, discharge diagnoses, and pharmaceutical sleep aid use.

RESULTS

Patients reported significantly worse nighttime sleep duration in hospital compared with home (mean 5.5 versus 7.0 hours per night, $p < 0.0001$). Sleep quality was poor, as measured by the VSH disturbance (mean 371), effectiveness (190), and supplementation (115) subscales. Variables independently associated with poorer sleep duration in multivariable regression include prior diagnosis of sleep disorder and multi-patient occupancy rooms. Age, sex, admitting diagnosis, length of stay, frequency of vital checks, and use of sleep pharmaceuticals during the index hospitalization were not associated with sleep duration. The most frequently reported reasons for poor sleep included noise (59%), nursing interruptions (30%), uncomfortable beds (18%), bright lights (16%), unfamiliar surroundings (14%), and pain (9%).

CONCLUSIONS

Sleep duration and quality for GIM inpatients is significantly worse in hospital than at home. There is a need to test non-pharmacologic interventions to address the most frequently identified factors causing poor sleep hygiene for GIM inpatients. Based on the results of this study, we plan to design a targeted non-pharmacologic intervention for supporting sleep of GIM inpatients.

Funding for this project was received from Alberta Health Services 2014 Quality Improvement Funding Competition.

Supervisor: Dr. Jennifer Ringrose

Back to Previous Page

Quality of Endoscopic Documentation in Cases of Barrett's Esophagus: A Retrospective Analysis

Maryam Soleimani, Clarence Wong
Supervisor: Dr. Clarence Wong

INTRODUCTION

Esophageal adenocarcinomas (EAC) are malignancies arising in the distal esophagus. The greatest risk factor for the development of EAC is the presence of Barrett's esophagus (BE), which is associated with chronic reflux and smoking. The five-year survival amongst patients with EAC is poor, and therefore screening, in the form of endoscopy, is of utmost importance in detecting BE, and preventing progression to EAC. Currently, there is significant inter-operator variability in the detection and reporting of endoscopic findings for BE. There are guideline recommendations, but no standardized reporting forms. The current standard of practice is to provide a score known as the Prague C&M (circumferential and maximum) criteria to determine the extent of BE. Biopsies and subsequent surveillance are done based on this score.

METHODS

We performed a retrospective chart review of adult patients referred to the Alberta Endoscopic Ablation Program between 2012-2015. We collected demographics, presence of BE risk factors, and specific qualitative and quantitative measures as provided on endoscopy and pathology reports. We also examined number of biopsies taken to determine if they were correct for the length of BE detected.

RESULTS

59 patients met criteria for inclusion in the study. Of these, over 80% had reflux symptoms, and 100% were on a proton pump inhibitor. Less than 50% of endoscopy reports provided location of biopsies or endoscopic landmarks, while only 37.9% reported Prague C&M criteria. This reflects a poor quality of endoscopic reporting that does not meet current standards. Three diagnoses of adenocarcinoma were missed on initial endoscopy, prior to referral.

CONCLUSIONS

There is significant inter-operator variability in the reporting of endoscopy findings in patients with BE. The creation of a standardized reporting form to be completed by the endoscopist at the end of the procedure may address some of these inconsistencies.

Supervisor: Dr. Clarence Wong

Back to Previous Page

Table 1: Results of patient demographics and qualitative analysis

Demographics			
Population: (n=59)	Males	Females	Mean age (years)
	47 (79.7%)	12 (20.3%)	61.5
BE Risk Factors:			
Risk Factor:	Smokers >2 alcoholic beverages/day Symptoms of GERD Patients on PPI	33 (55.9%) 6 (10.2%) 51 (86.4%) 59(100%)	
Quality of Endoscopic Reporting:			
Location of biopsies provided:	28 (48.3%)		
Endoscopic landmarks reported:	24 (42.9%)		
Photo-documentation:	10 (17.5%)		
Description of mucosal appearance:	29 (51.8%)		
Prague C&M criteria reported:	22(37.9%)		
Diagnoses:			
Diagnosis at referral:			
BE:	13 (22.0%)		
LGD:	11 (19.3%)		
HGD:	8 (13.6%)		
Indefinite dysplasia:	13 (22.0%)		
Adenocarcinoma:	7 (11.9%)		
MFLGD:	2 (3.4%)		
Nodular BE:	1 (1.7%)		
Final diagnosis after referral to ablation program:			
BE:			
HGD:	2 (3.6%)		
LGD:	12 (21.4%)		
Indefinite dysplasia:	10 (17.9%)		
No dysplasia:	2 (3.6%)		
Adenocarcinoma:	19 (33.9%)		
MFLGD:	7 (12.5%)		
MFHGD:	1 (1.8%)		
Normal:	1 (1.8%)		
	2 (3.6%)		

Back to Previous Page

Secular trends in incidence and mortality of acute venous thromboembolism: The AB-VTE population based study.

Ghazi S. Alotaibi, MD, Cynthia Wu, MD, FRCPC, Ambikaipakan Senthilselvan, MSc PhD, M. Sean McMurtry, MD PhD FRCPC
Supervisor: Michael Sean McMurtry, Cynthia Wu

INTRODUCTION
Venous thromboembolism (VTE) is a major cause of morbidity and mortality, and comprehensive studies profiling the epidemiology and pattern of health services use are needed. In this study we provide contemporary estimates of VTE incidence and case fatality over the past decade.

METHODS
We developed a population-based VTE dataset by linking 6 administrative health databases in Alberta, Canada from April 1, 2002 to March 31, 2012. We defined acute symptomatic cases using a validated algorithm and used Poisson regression to model annual VTE counts.

RESULTS
We identified 31,656 cases of acute symptomatic VTE between April 1, 2002, and March 31, 2012. The age and sex adjusted incidence rate of VTE was 1.38 (95% CI: 1.37, 1.40) per 1000 person-years. For pulmonary embolism (PE) it was 0.38 (95% CI: 0.36, 0.40) per 1000 person-years and for deep vein thrombosis (DVT) it was 1.0 (95% CI: 0.99, 1.1) per 1000 person-years. The adjusted model showed no significant change in the incidence of VTE during the study period. The 30-day case fatality rate of VTE was 2.0% (95% CI: 1.89, 2.21) and was almost doubled in patients with PE 3.9% (95% CI: 3.50, 4.33). The 1-year case fatality was 9.2% (95% CI: 8.88, 9.52) for VTE and 12.9% (95% CI: 12.2, 13.6) for patients with PE. The case fatality increased with increasing subject age. The 1-year and 5-years survival after first acute VTE were similar in patients with unprovoked and provoked events. However, in patients with cancer associated thrombosis, the 1-year and 5-years survival was 66% (95% CI: 64.71% to 67.29%) and 46% (95% CI: 43.28% to 48.72%) respectively.

CONCLUSIONS
The incidence of acute venous thromboembolism remained unchanged over a 10-years period. However, the case fatality of VTE is substantial.

Supervisor: Dr. Michael Sean McMurtry, Cynthia Wu

Back to Previous Page

Histological validation of hippocampal subfield segmentation

Steve TA(1), Yasuda CL(2), Coras R(3), Blumcke I(3), Livy DJ(1), Malykhin NV(1), Gross DW(1)
Supervisor: Dr. Donald Gross

INTRODUCTION

Recent findings have demonstrated that hippocampal subfields can be selectively affected in different disease states, which has led to efforts to segment the human hippocampus with in vivo magnetic resonance imaging (MRI). However, no studies have examined the histological accuracy of subfield segmentation protocols.

METHODS

Ultra-high resolution ex vivo MRI (voxel size 0.2 X 0.2 X 0.5 mm3) was performed on six cadaveric hippocampal specimens (22 blocks) prior to histological processing. The hippocampal bodies were segmented into subfields based on histological criteria. A novel method was developed using mean percentage of the total stratum lacunosum moleculare (SLM) distance to define three subfield boundaries. Measurements were then determined using the novel method and according to three previously published techniques (Figure 1) and compared to the gold standard using the Bland-Altman method and calculation of intra-class correlation coefficient (ICC). The novel method was then applied to ex vivo MRI (Figure 2) and compared to histological measurements by calculation of ICC.

RESULTS

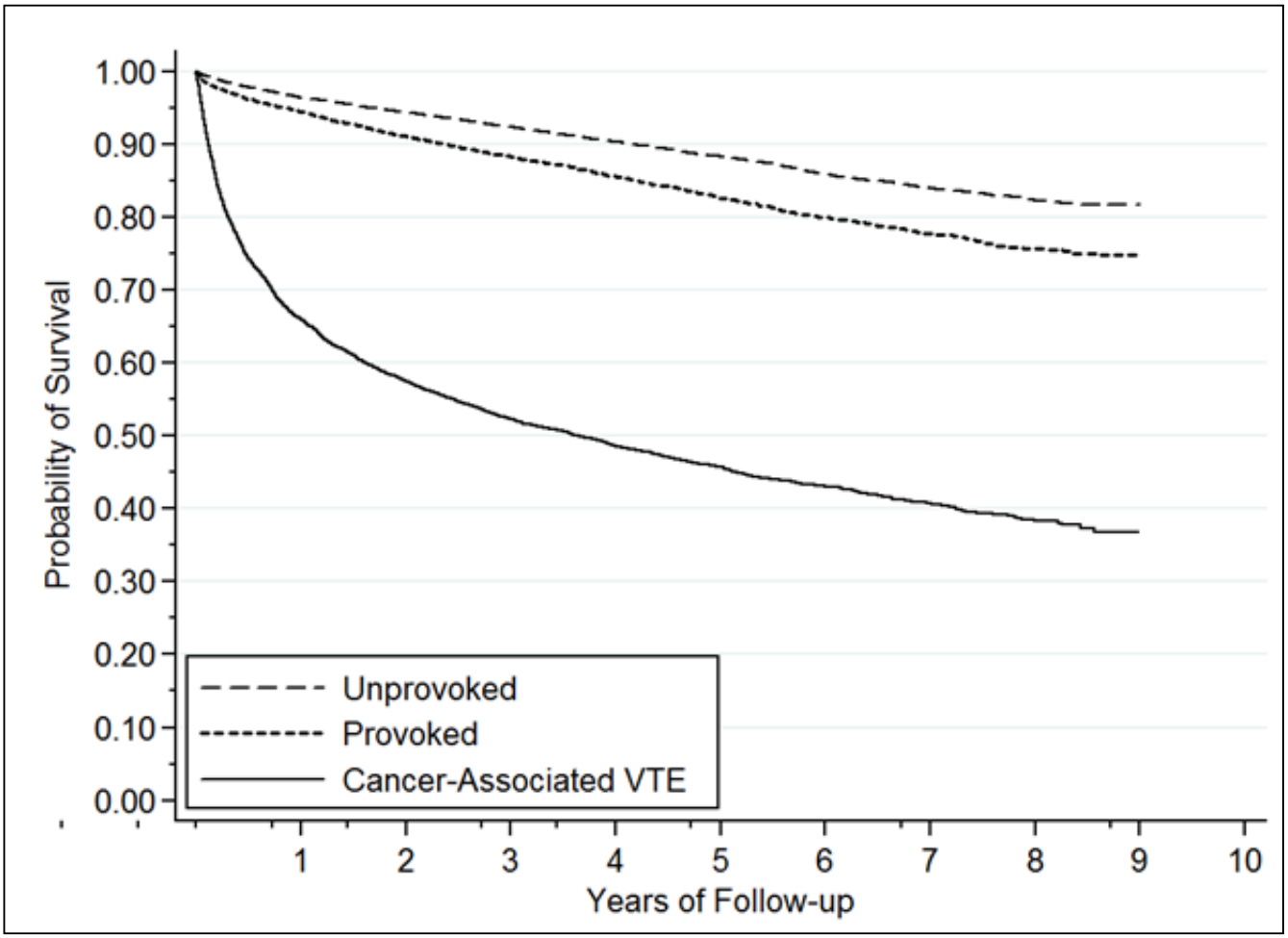
The novel method provided accurate measurements for CA1/CA2 (ICC = 0.93) and CA2/CA3 (ICC = 0.97), but not for Subiculum/CA1 (ICC = -0.04). Accuracy was poorer using previous techniques for CA1/CA2 (maximum ICC = 0.81) and CA2/CA3 (maximum ICC = 0.88), with the previously reported techniques also performing poorly in defining the Subiculum/CA1 boundary (maximum ICC = 0.00). Ex vivo MRI measurements using the novel method were strongly correlated with direct measurements of SLM length (ICC = 0.88), CA1/CA2 boundary (ICC = 0.69) and CA2/CA3 boundary (ICC = 0.72), but not for Subiculum/CA1 boundary (ICC = -0.06).

CONCLUSIONS

The CA1/CA2 and CA2/CA3 boundaries can be accurately determined using the novel method. Our study provides limits for the Subiculum/CA1 boundary which could be used to define a Subiculum/CA1 transition zone to allow isolated Subiculum and CA1 subfield measurements.

Supervisor: Dr. Donald Gross

Back to Previous Page



Back to Previous Page

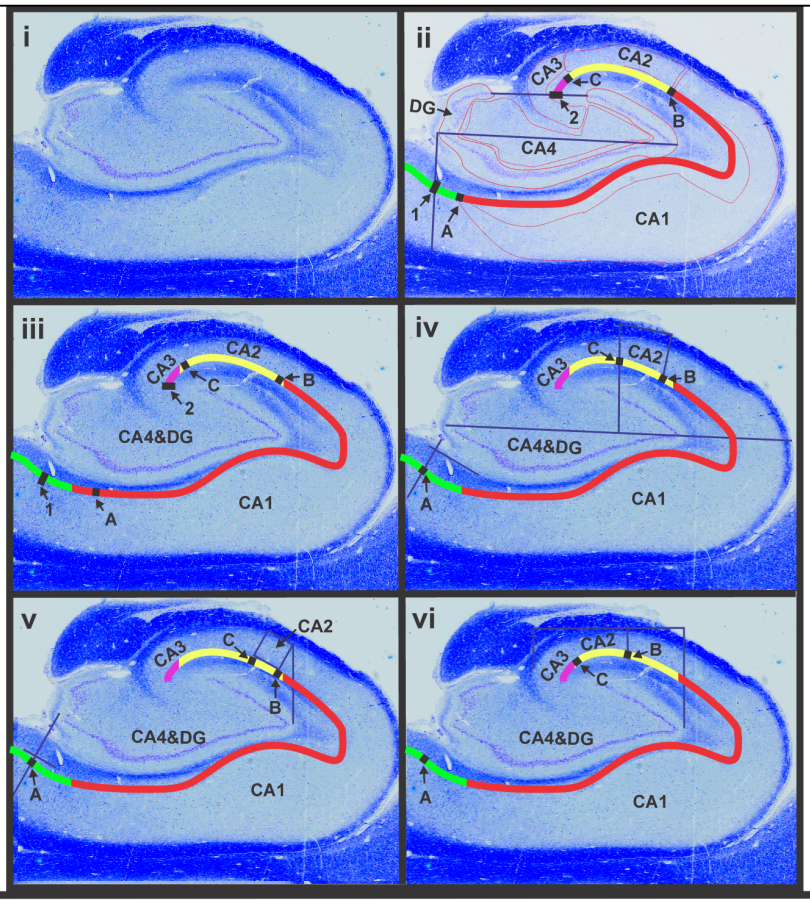


Figure 1 - Development of novel method and comparison to previous techniques:
i) Histological section from a cadaveric hippocampus (the same section is displayed in all panels). ii) Distances of three hippocampal subfield boundaries [Subiculum/CA1 (A), CA1/CA2 (B), and CA2/CA3 (C)] along a line from the superficial hippocampal sulcus (1) to the blades of the dentate gyrus (2) were directly measured. The stratum lacunosum moleculare (SLM) was colour-coded according to histologically defined subfield locations in this specific section (Subiculum, green; CA1, red; CA2, yellow; CA3, pink). For all subsequent panels, the histologically segmented SLM is projected to compare the gold standard to each of the other methods applied. iii) Novel method: Mean percentages of the total SLM length were used to determine the distances of three subfield boundaries [Subiculum/CA1 (A), CA1/CA2 (B), and CA2/CA3 (C)] from the superficial hippocampal sulcus (1). iv-vi) Previous techniques: The distances of three subfield boundaries [Subiculum/CA1 (A), CA1/CA2 (B), and CA2/CA3 (C)] from the superficial hippocampal sulcus (1) were determined according to previously published segmentation protocols [iv: Technique 1, v: Technique 2, vi: Technique 3]. For techniques 1-3 the defined CA1 region includes a substantial amount of subiculum. For technique 3, CA1 includes a substantial amount of CA2. For techniques 1 and 2, CA3 includes a substantial amount of CA2.

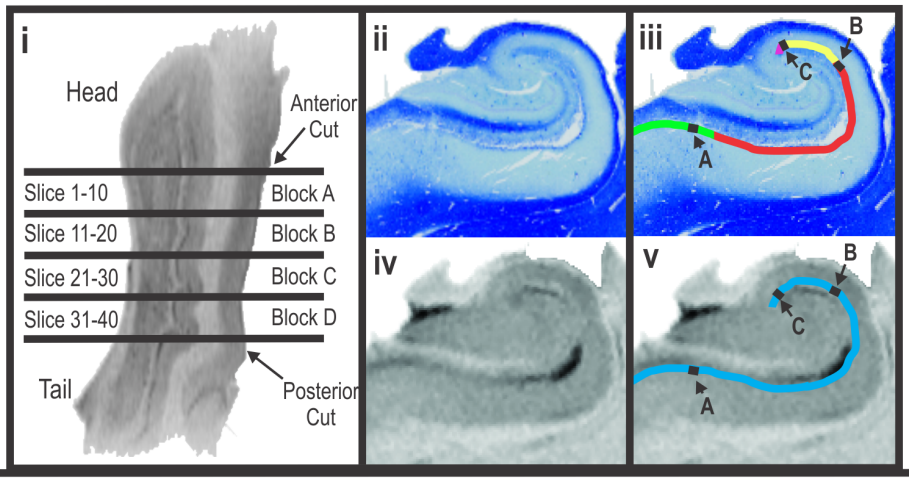


Figure 2 - Coregistration of ex vivo MRI with histology:
Ultra-high resolution ex vivo MRI (voxel size 0.2 X 0.2 X 0.5 mm^3) was performed prior to histological sectioning.
i) Anatomical blocks of the hippocampal body (A-D) were coregistered to ex vivo MRI slices (1-40) using fiducial markers (anterior and posterior cuts). Corresponding histological (ii) and ex vivo MR images (iv) were then identified by iteratively matching features of the hippocampal architecture. iii) The stratum lacunosum moleculare (SLM) was colour-coded according to histologically defined subfield locations in this specific section (Subiculum, green; CA1, red; CA2, yellow; CA3, pink). v) The SLM was manually traced based on differences in signal intensity between grey and white matter (blue). iii and v) The novel method was applied to histology (iii) and ex vivo MRI (v): Mean percentages of the total SLM length were used to determine the location of three subfield boundaries: [Subiculum/CA1 (A), CA1/CA2 (B), and CA2/CA3 (C)].

Back to Previous Page

Targeting Endoplasmic Reticulum Stress With 4-Phenylbutyrate Improves Mitochondrial Metabolism and Lung Function in Pulmonary Fibrosis

Vikram Gurtu, Roxane Paulin, Christopher White, Adam Kinnaird, Aristeidis Boukouris, Sotirios Zervopoulos, Trevor Stenson, Darren Freed, Jayan Nagendran, and Evangelos Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a deadly disease driven by excessive fibroblasts proliferation. Early data suggest that IPF is characterized by a) a cancer-like suppression of mitochondria that promotes proliferation and inhibits apoptosis and b) endoplasmic reticulum stress (ERS). We have shown that ERS suppresses mitochondria by decreasing mitochondrial calcium. We hypothesized that the natural chemical chaperone 4-phenylbutyrate (PBA), an ERS inhibitor, will be beneficial in IPF.

METHODS

We studied 2 models: a mouse IPF model (intra-tracheal bleomycin) and human IPF lungs explanted from transplant recipients, immediately studied with ex vivo lung perfusion (EVLP): bronchi connected to a ventilator; pulmonary arteries perfused with recirculating modified Krebs-Henseleit buffer. We studied control, bleomycin, and treated mice receiving PBA in drinking water 2 weeks after bleomycin. We measured lung compliance/elastance (Flexivent platform) and fibrosis (histology). For EVLP we studied 5 IPF lungs, measuring mitochondrial respiration (Seahorse analyzer) and indices of ERS (immunoblots) before/after 1-hour treatment with 4-PBA.

RESULTS

Static pulmonary elastance was increased in bleomycin compared to control mice (24.9 vs 13.3cmH2O/mL) but reduced in PBA-treated mice (16.1cmH2O/mL). Fibrotic grade was also reduced in PBA-treated mice lungs. PBA also decreased ERS in fibroblasts isolated from human lungs in vitro. In EVLP IPF lungs, 4-PBA increased O2 consumption in 3 of the IPF lungs by 30-72%.

CONCLUSIONS

Chronic 4-PBA treatment can improve lung function in pulmonary fibrosis by limiting ERS and mitochondrial inhibition in mice and at least in some IPF patients. IPF is a multifactorial complex disease and the mitochondria-ERS axis may not be important in all patients. Exploration of this variability will allow precision-medicine approaches in future trials with 4-PBA, a drug that has already been used in clinical trials (diabetes). Human EVLP is an ideal platform in which to study drug responses and biomarkers prior to clinical translation.

Supervisor: Dr. Evangelos Michelakis

Back to Previous Page

Routine Coronary Artery Bypass of Angiographically Borderline Coronary Artery Stenoses is not Associated with Improved Survival

Senaratne J, Norris CM, Graham MM, Nagendran J, Freed DH, Afilalo J, Van Diepen S
Supervisor: Dr. Sean Van Diepen

INTRODUCTION

Coronary artery bypass grafting (CABG) improves outcomes in patients with multi-vessel coronary artery disease. Bypass of angiographically significant lesions ≥70% is recommended yet there is little evidence to guide decision making for angiographically borderline 50-69% lesions (ABL), which has led to wide variability in practice patterns.

METHODS

Between 2007 and 2013, 3,195 patients in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry underwent isolated first CABG with at least 2 distal anastomoses. Patients with an isolated ABL (50-69%) of the proximal segment of a major epicardial coronary vessel (excluding the left main) on the pre-operative angiogram were included in the study. The primary outcome of interest was long-term mortality.

RESULTS

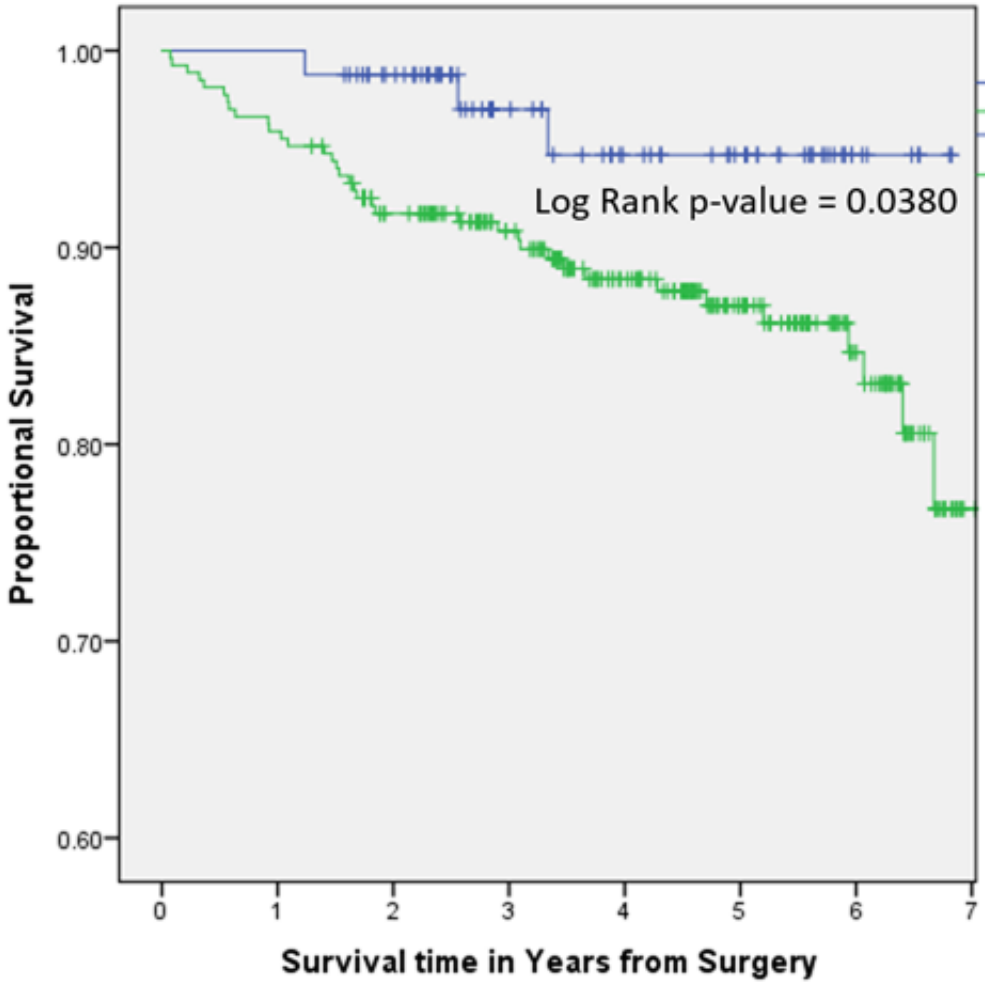
Among the 350 patients with an ABL, 268 (76.6%) were surgically bypassed. Mean follow-up was 4.2 ± 1.7 years. Patients with a bypassed ABL tended to be older (62.5 vs 66.1 years, p=0.01) but were otherwise similar in terms of sex, comorbidities, diabetes, ejection fraction, and number of coronary stenoses. Cardiopulmonary bypass time was longer in patients with bypassed ABL (104.2 vs 90.4 minutes, p<0.001). Compared to non-bypassed ABL, bypassed ABL was associated with a trend towards increased long term mortality (adjusted odds ratio 2.96: 95% confidence interval, 0.90 – 9.68, p=0.07). Figure 1 shows the time to all-cause mortality from surgery. No differences were observed in either 30-day (0.0% vs 1.1%, p=0.336) or 1-year mortality (0.0% vs 4.1%, p=0.062). No interactions between major epicardial ABL vessel location and mortality were identified. Repeat revascularization of ABL bypass grafts was numerically higher (0.0% vs 4.1%, p = 0.107).

CONCLUSIONS

In a large unselected cohort of patients with ABL, bypass of these 50-69% lesions is frequently performed and not associated with improved long-term survival. Our findings suggest that the routine surgical revascularization of ABLs may not be warranted.

Supervisor: Dr. Sean Van Diepen

Back to Previous Page



Number at risk by year	0	1	2	3	4	5	6	7
No Borderline Bypass	82	82	73	46	34	26	7	7
Borderline bypass	268	257	230	196	154	104	54	2

Back to Previous Page

Prognostic Impact of CD3 Infiltrating T-cells in the Tumor Microenvironment with Clinical Factors for Solid Organ Transplant (SOT) Recipients with Post-Transplant Lymphoproliferative Disorders (PTLD)

Stubbins, R.J.1, Lai, R.2, Preiksaitis, J.3, Zhu, J.2, Peters, A.4
Supervisor: Dr. Anthea Peters

INTRODUCTION

Prognostication in post-transplant lymphoproliferative disorders (PTLD) is limited to clinical factors, with no validated tissue biomarkers. It is suggested that the degree of CD3 positive cytotoxic T-cell infiltrate in the tumor microenvironment is predictive of overall survival (OS) in PTLD, given the role of immune competence in PTLD pathogenesis.

METHODS

A retrospective analysis of 146 solid-organ transplant recipients with PTLD was performed for clinical prognostic variables and OS. For 43 patients, CD3 infiltrate was determined by a blinded pathologist with a standardized scoring system (integer scale 0 – 3), utilizing formalin-fixed tissue stained for CD3 by immunohistochemistry. Survival analysis was done by Cox regression, including a Kaplan-Meier (KM) estimator for CD3 infiltrate, with between group differences tested by a Pearson's chi-square test.

RESULTS

Histology subtypes included early (n = 7), polymorphic (n = 17), monomorphic, (n = 85) Hodgkin, (n = 8) and unknown. (n = 29) Median OS was 41 months, with 71 (49%) deceased. Clinical factors identified by univariate analysis include: age < 18 at transplant ($p = 0.017$), monomorphic histology ($p = 0.010$), ECOG 3-4 ($p = 0.027$), stage 3-4 ($p < 0.001$), elevated LDH ($p = 0.006$), extranodal disease ($p = 0.035$), IPI 3-5 ($P < 0.001$), marrow involvement ($p = 0.017$), and lymphocytes < 1.0 at diagnosis. ($p = 0.004$)

Dense CD3 infiltrate (score 2-3) was associated with improved OS by KM analysis ($p = 0.048$) and a trend towards significance by univariate Cox regression. (HR 0.401, $p = 0.056$) Dense CD3 infiltrate was associated with non-monomorphic histology ($p < 0.001$), but not EBER status. ($p = 0.154$)

CONCLUSIONS

The degree of CD3 infiltrate in the tumor microenvironment shows promise as a potential prognostic biomarker for SOT patients with PTLD. Clinical prognostic factors remain dominant. Further study by expanding the number of patients assessed for CD3 infiltrate is warranted.

Supervisor: Dr. Anthea Peters

Back to Previous Page

Effect of Cuff Design on Auscultatory and Oscillometric Blood Pressure Measurements

Ringrose Jennifer1, Mclean Donna,2 Ao Peter,1 Yousefil Farahnaz,1 Sankaralingam Sownd, Millay Jack,3 Padwal Raj1,4,5
Supervisor: Dr. Raj Padwal

INTRODUCTION

Two-piece blood pressure (BP) cuffs, which contain a removable bladder enclosed within a fabric shell, are the historical cuff standard. Use of one-piece cuffs, in which the bladder is formed by a potential space within the fabric shell, is increasing. Substituting one-piece for two-piece cuffs has an unknown effect on measurement accuracy. We compared these cuff types in a two-phase study using auscultatory (Phase 1) and oscillometric (Phase 2) techniques.

METHODS

Community-dwelling, consenting subjects (aged ≥18y) with BP levels between 80-220 mmHg/50-120 mmHg and arm circumferences between 25-43 cm were studied using the International Standards Organization (ISO) 2013 protocol (with modifications). A Baum two-piece cuff was used as the reference standard, to which a one-piece Welch Allyn cuff was compared. In Phase 1 (two-observer auscultation with a mercury sphygmomanometer), 88 subjects were required to obtain 255 paired BP determinations. In Phase 2 (oscillometric measurement with a Spacelabs 90207 device), 85 subjects were studied. Each study phase was analyzed separately using paired t-tests.

RESULTS

For the auscultatory phase, mean age was 54.2±20.5 years, mean arm circumference was 29.9±3.7 cm, 60% were female and 32% had a past history of hypertension. Mean BP levels for the one-piece cuff were lower than the two-piece cuff (115.5±15.5/66.4±9.3 vs. 117.8±15.2/67.9±9.2; difference of -2.4±3.6/-1.5±2.4; p-values<0.0001 for both comparisons). For the oscillometric phase, mean age was 52.8±20.8 years, mean arm circumference was 29.4±3.9 cm, 67% were female, and 38% had hypertension. Mean BPs were lower for the one-piece compared to the two-piece cuff (116.5±12.8/67.1±8.1 vs. 120.8±13.5/70.4±8.5; difference of -4.4±3.6/-3.3±2.7; p-values<0.0001 for both).

CONCLUSIONS

Mean BP is lower when one-piece cuffs are used instead of two-piece cuffs. Differences are greater with oscillometry. Therefore, when performing validation studies and measurements for clinical purposes, the potential effect of cuff type should be taken into account.

Supervisor: Dr. Raj Padwal

Back to Previous Page

CONTACT ALLERGY TO THE TOPICAL ANESTHETIC PRAMOCAINE IS SURPRISINGLY COMMON AMONG PATIENTS BEING PATCH TESTED AT A TERTIARY DERMATOLGY CLINIC

John F. Elliott, Mariam Abbas, and Kunimasa Suzuki
Supervisor: Dr. John Elliott

INTRODUCTION

Many over-the-counter anti-itch and anti-inflammatory products contain topical anaesthetics, yet paradoxically the patients who use these products the most (i.e. chronic eczema patients) often become allergic to topical anaesthetics. Currently the molecule of choice for these patients is pramocaine (also called PramoxineHCl), since this topical anaesthetic is considered to be the least sensitizing. However, this notion may not be true, but rather due simply to the fact that very few contact dermatitis patients have ever been tested to pramocaine—since commercial patch test material for this anaesthetics have not been available.

METHODS

To find the optimum patch test material to detect pramocaine sensitivity, we prepared in house four different pramocaine mixtures (1% and 2% in petrolatum and water) using high purity chemicals (Sigma), and tested all four on a known pramocaine allergic patient who had been identified because he was strongly positive to his own pramocaine-containing products. Using the optimum test material (2% in petrolatum), we patch tested 495 consecutive patients between May 2014 and August 2015. Patch test results were evaluated at 48 and 96h, using the ICDRG scoring system. Descriptive statistics, Clopper-Pearson Exact 95% Confidence Intervals, and incidence rates were calculated.

RESULTS

Overall fifteen patients out of the 495 were sensitized to pramocaine. Fourteen patients demonstrated a 1+ response and one patient had a 2+ response (3.03% overall response [95% CI: 1.71%-4.95%]). Gender differences were not statistically significant. The average age of positive patients was 39 years (range 11-69 years). Four patients showed concomitant responses to an amide anesthetic agent: two to dibucaine and two to lidocaine.

CONCLUSIONS

Contact sensitization to pramocaine was previously thought to be a rare event, but in fact it occurs relatively commonly. In chronic eczema patients, patch testing to Pramocaine/PramoxineHCl should be considered since it is present in many over-the-counter products.

Supervisor: Dr. John Elliott

Back to Previous Page

Correlation of aging with expression of thrombotic protein Von Willebrand Factor (VWF)

Radya Abdualla
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Expression of Von Willebrand Factor (VWF) is restricted to endothelial cells and megakaryocytes. VWF plays a crucial role in maintaining primary hemostasis. In addition, there are pathological and physiological conditions, which alter the level of VWF in the circulation and the expression pattern of VWF in vasculature. Unregulated increase in VWF levels may contribute to increased thrombogenicity. Since increased thrombogenicity is observed with aging, we explored whether aging is associated with alterations in levels and/or pattern of VWF expression.

METHODS

This study compared circulating VWF levels in the blood of young and aged mice and rats, using Elisa. Additionally, Immunofluorescent confocal microscopy as well as RT-PCR analyses were used to determine RNA levels and the expression pattern of the VWF protein, combined with the endothelial marker CD31 and micro vessels marker (Isolectin-GS-IB4), in the brains, livers, hearts, kidneys and lungs of young and aged mice.

RESULTS

With age VWF expression at RNA levels increased in brains, lungs, and livers of mice, but not other organs. Also circulating VWF protein levels increased in blood of aged rats. Moreover, the endothelial staining intensity of VWF increased in micro and macro vessels of brains, lungs, and livers of aged compared to young mice.

CONCLUSIONS

With aging, VWF levels are increased in circulation. Furthermore, an altered VWF expression pattern, specifically increased expression in microvasculature of brain, lung, and liver, is observed. Overexpression of VWF in circulation and microvascular beds of distinct organs as a result of aging may contribute to vascular diseases such as thrombosis.

Supervisor: Dr. Nadia Jahroudi

Back to Previous Page

The Alberta Vascular Risk Reduction Community Pharmacy Project: RxEACH

Ross T. Tsuyuki 1, Brenda R Hemmelgarn 2, Charlotte A. Jones 3, Yazid N. Al Hamarneh1.
Supervisor: Ross Tsuyuki

INTRODUCTION

Despite the risk associated with hypertension, diabetes, dyslipidemia, and smoking, these cardiovascular disease (CVD) risk factors remain poorly identified and controlled.
To evaluate the effect of a community pharmacy-based case finding and intervention program on estimated cardiovascular risk.

METHODS

Design: Randomized controlled trial.
Setting: 56 community pharmacies across Alberta.
Population: Adults at high risk for CVD events, including those with diabetes, chronic kidney disease, vascular disease and/or Framingham score > 20% who have at least one uncontrolled risk factor (hypertension, LDL-cholesterol (LDL-c), HbA1c, or current smoking).
Randomization: Participants were randomized (1:1 basis) into advanced or usual care groups.
Advanced care: Pharmacists provided participants with:
- Physical and laboratory assessments
- Individualized CVD risk assessment and education
- Pharmacists prescribed where appropriate to achieve treatment targets
- Regular monthly follow-ups for 3 months

Usual care: Usual pharmacist care with no specific intervention for 3 months.
Primary outcome: The difference in change in estimated CVD risk between advanced and usual care groups, calculated using a relevant risk calculator based on participants' co-morbidities (Framingham, International, or UKPDS).

RESULTS

We enrolled 723 patients. Median age was 62 years (interquartile range 54-69), 57% were male and 27% were smokers. After adjusting for baseline values, the difference in change in CVD risk was 21% ($p<0.001$): a change of 0.2 mmol/L in LDL-c ($p<0.001$), 9.4 mmHg in systolic blood pressure ($p<0.001$), 0.92% in HbA1c ($p<0.001$), and 20.2% in smoking cessation ($p=0.002$) between advanced and usual care groups

CONCLUSIONS

This is the first large randomized trial of CVD risk reduction in community pharmacy settings. Patients in the advanced care group were 21% less likely to have a heart attack, stroke, or peripheral artery disease when compared to those in the usual care group. RxEACH provides evidence for the benefit of pharmacist care on both global CVD risk and individual risk factors.

Back to Previous Page

The impact of introducing an Enhanced Recovery After Surgery (ERAS) protocol in Alberta on individuals with diabetes: an interrupted time series analysis

Zaina Albalawi, Jeff Bakal, Leah Gramlich, Peter Senior, Finlay McAlister
Supervisor: Finlay McAlister

INTRODUCTION

The prevalence of diabetes in patients undergoing surgery ranges from 10% to 40%. It is well recognized that individuals with diabetes have higher rates of complications postoperatively, and longer hospital stays compared to patients without diabetes. Enhanced Recovery After Surgery (ERAS) is an evidence-based multimodal surgical care pathway that has been shown to improve postoperative complications and length of stay in patients without diabetes. This study aims to evaluate the impact of ERAS implementation in Alberta.
The primary outcome of interest is adjusted length of stay (LOS). Secondary outcomes include postoperative surgical and infectious complications, and 30-day readmission rates.

METHODS

Statistical Analysis: The data will be analyzed as an interrupted time series. The impact of ERAS protocol implementation will be evaluated in a series of pre-post comparisons for patients with and without diabetes undergoing elective colorectal surgery pre versus post ERAS implementation at the six main surgical sites in Alberta. Adjusted LOS will be examined monthly at the 6 surgical sites from September 2011 to December 2015 along with complication and 30-day readmission rates. Multivariate linear regression modeling will be used for LOS, and logistic regression for the other binary outcomes. Autocorrelation, partial autocorrelation and inverse autocorrelation functions will be assessed for model parameter appropriateness and seasonality. Stationarity will be assessed using the autocorrelation function and the augmented Dickey–Fuller test. All statistical analysis will be done using STATA, version 14.0 (Stata Corporation, College Station, Texas).

RESULTS

Analysis in-process

CONCLUSIONS

Pending

Supervisor: Dr. Finlay McAlister

Back to Previous Page

Lipopolysaccharide and Polyinosinic:Polycytidylic Acid attenuate Interleukin –13 induced Eotaxin-3

Dhaifallah Alotaibi and Harissios Vliagoftis
Supervisor: Harissios Vliagoftis

INTRODUCTION

Airway epithelium participates in asthma pathogenesis through the production of a wide range of mediators including eosinophil chemotactic factors. Interleukin-13 (IL-13) is a central effector cytokine in asthma. IL-13 may promote eosinophilic inflammation, airway hyper-responsiveness, mucus secretion, epithelial damage and fibrotic changes in the airways. IL-13 stimulates bronchial epithelial cells to release eotaxin-3 (CCL26), a potent chemoattractant for eosinophils, a hallmark of asthma. Epithelial cells also express Toll-like receptors (TLRs), which detect microbial pathogens and play an important role in inflammation. We hypothesize that bacterial and viral products through TLR activation decrease the effect of IL-13 on CCL26 secretion from airway epithelial cells.

METHODS

We used poly I:C (TLR3 ligand) and LPS (TLR-4 ligand) to mimic the effects of viruses and bacteria respectively on the airway epithelium. The human bronchial epithelial cell line BEAS-2B was stimulated with poly I:C (25 ug/ml), or LPS (10 ug/ml) alone or in combination with IL-13 (20 ng/ml) for 24 hrs. RNA was extracted and CCL26 mRNA levels measured using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

RESULTS

IL-13 strongly up-regulated CCL26 mRNA expression (33.39 ± 1.87 fold over unstimulated cells, n=3). However, when the cells were cultured with IL-13 and LPS (10 ug/ml) or Poly I:C (25 ug/ml), this increased CCL26 expression was strongly down regulated (1.13±0.20 and 6.56±1.87 fold over unstimulated cells respectively, n=4).

CONCLUSIONS

Our study indicates that TLR3 and TLR4 ligands attenuate the effects of IL-13 on CCL26 expression in epithelial cells. Further studies will investigate the mechanisms mediating this attenuation.

Supervisor: Dr. Harissios Vliagoftis

Back to Previous Page

Short- and Long-Term Mortality after Pulmonary Embolism in Patients with and without Cancer

Ghazi S. Alotaibi, MD, Cynthia Wu, MD, FRCPC, Ambikaipakan Senthilselvan, MSc PhD, M. Sean McMurtry, MD PhD FRCPC
Supervisor: Michael Sean McMurtry, Cynthia Wu

INTRODUCTION

Pulmonary embolism (PE) is a major cause of mortality and morbidity. It is known that the risk of death varies by provoking factors, however, it is unknown if the risk of death persists beyond the initial diagnosis among patients with cancer and other provoked patients. In this study, we aimed to investigate the effect of cancer on overall, short- and long-term mortality in a cohort of consecutive incident PE patients.

METHODS

Using the administrative health care databases of the Canadian province of Alberta, we identified all incident cases of pulmonary embolism between 2004 and 2012 and stratified them by provoking factors (unprovoked, provoked, and cancer-associated). Multivariate Cox survival model was used to estimate the hazard ratios of short- and long-term death.

RESULTS

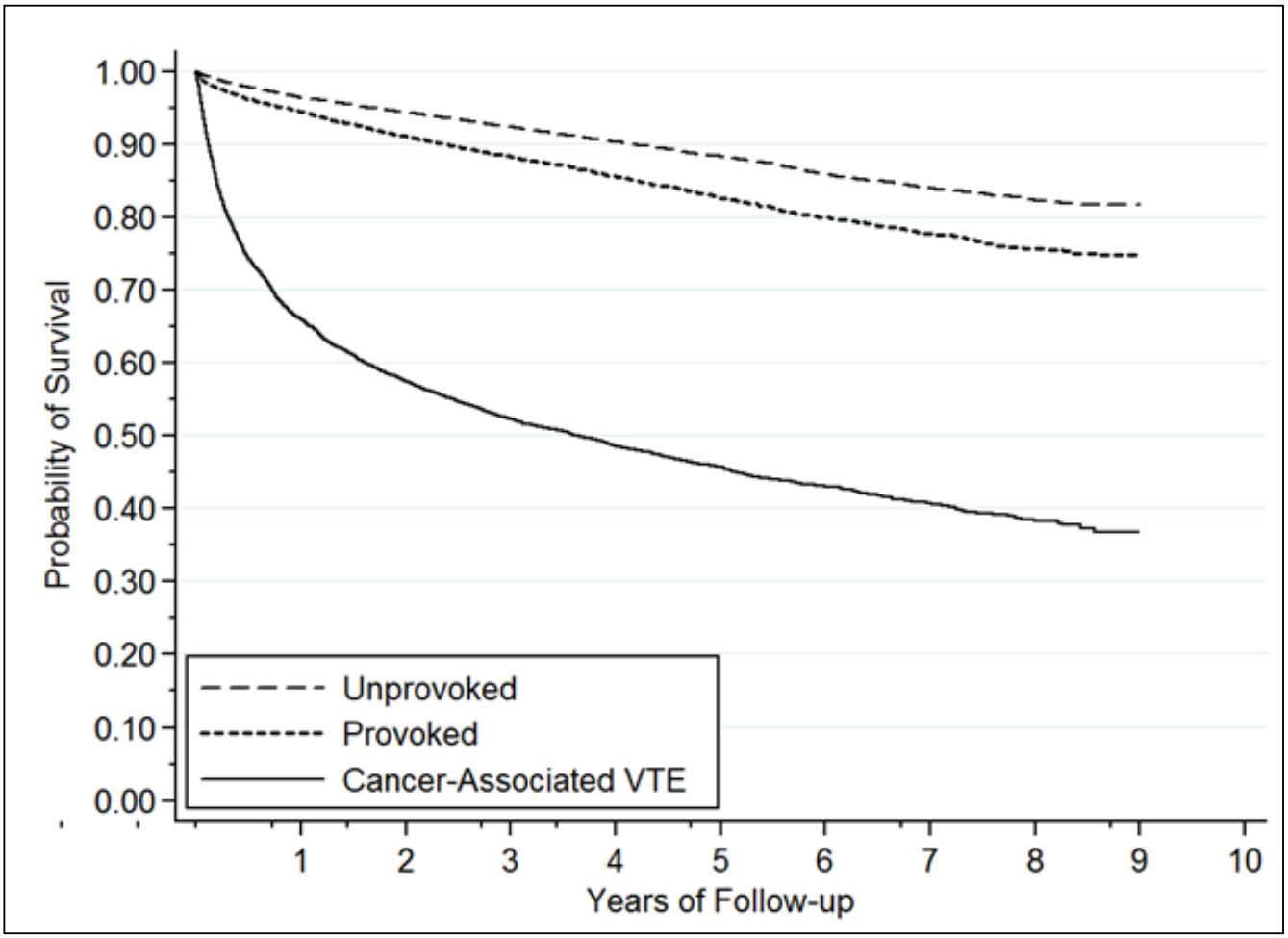
We identified 8641 patients with PE, among which 42.2% were unprovoked, 37.9% were provoked and 19.9% were cancer–associated. The 1-year and 5-year survival probabilities were 61% (95% CI: 57-64) and 39% (95% CI: 36-43) in cancer-associated PE patients, 93% (95% CI: 92-94) and 80% (95% CI: 78-81) in provoked PE patients, and 94% (95% CI: 93-95) and 85% (95% CI: 83-87) in unprovoked PE patients, respectively. Compared to patients with unprovoked events both short-term and long-term survival in patients with cancer associated PE have significantly higher observed risk of all-cause mortality in all age groups, P-value <0.001. In contrast, compared to the unprovoked PE group, patients with provoked events had similar short- and long-term hazard of death.

CONCLUSIONS

PE is still a common condition with a high mortality in all risk groups, however, patients with cancer have a substantial risk of short-term mortality compared to patients with unprovoked PE.

Supervisor: Dr. Michael Sean McMurtry, Cynthia Wu

Back to Previous Page



Back to Previous Page

Cockroach Extract Down-regulates IL-13-Induced Eotaxin-3 mRNA Expression in an Airway Epithelial Cell Line

Khadija Alzahrani, Vivek Gandhi, Cheryl Laratta, Drew Nahirney, Harissios Vliagoftis
Supervisor: Dr. Harissios Vliagoftis

INTRODUCTION

Interleukin-13 (IL-13) is a central mediator in asthma. It enhances mucus production, bronchial hyper-responsiveness and, smooth muscle proliferation. IL-13 also induces eotaxin-3 (CCL26) production, a potent eosinophil chemoattractant, from airway epithelial cells. Sensitization to cockroach allergens has been associated with asthma severity in many studies and cockroach extract (CE) has pro-inflammatory effects on airway epithelial cells. We hypothesize that cockroach extract enhances IL-13-mediated CCL26 upregulation in airway epithelium.

METHODS

Human bronchial epithelial cells, BEAS-2B, were cultured in pre-coated multi-well plates until confluent. Cells were then cultured for 24 hrs. with basal media (media without growth factors) and then treated with IL-13 or CE alone or with IL-13 and CE together for another 24 hrs. CCL26 mRNA levels were assessed using qRT-PCR.

RESULTS

IL-13 increased CCL26 mRNA levels in BEAS-2B cells 57.71 ± 20.19 fold compared to unstimulated cells (n=6). CE had no effect on its own but when cells were treated with IL-13 in the presence of CE, CCL26 mRNA level increased only 2.4 ± 0.7 fold over control cells (n=6). This effect was dependent on the protease activity of CE since heat inactivated CE could not decrease the effect of IL-13 on CCL26 mRNA levels. PAR-2 activating peptides also did not decrease the effect of IL-13, and if anything they showed a trend towards increasing the IL-13 effect on CCL26 mRNA, indicating that the CE effect is not mediated through PAR-2 activation.

CONCLUSIONS

CE decreases the IL-13-mediated CCL26 mRNA upregulation in airway epithelial cells. CE is a whole body extract that contains multiple allergenic and non-allergenic proteins from cockroach in addition to microbial elements. Further work is required to identify which of these CE components is responsible for the effect we described here.

Supervisor: Dr. Harissios Vliagoftis

Back to Previous Page

Effects of Metronidazole on Circulatory Dysfunction in Patients with Cirrhosis.

Aditi Amin, MPH, MD; Divya Shah; Lourdes Cabrera-García MD; Michelle Carbonneau, RN, NP; Kimberly Newnham, RN, NP; Puneeta Tandon, MD., Juan G. Abraldes, MMSc, MD.
Supervisor: Dr. Juan G. Abraldes

INTRODUCTION

Hepatic encephalopathy (HE) affects 50-70% of cirrhotic patients. Lactulose is first-line therapy in HE prevention. Second-line therapy includes antibiotics, such as rifaximin (RIF). While evidence supports RIF, it is expensive. Metronidazole (MET) has been used as an alternative, though supporting evidence is limited.

Data from our group suggests that the gut-derived metabolite propionate contributes to the circulatory dysfunction (CD) in cirrhosis. Since MET impacts propionate production, we hypothesize that MET could improve CD.

1) Primary outcome: HE episodes after initiating MET.

2) Secondary outcomes: mean arterial pressure (MAP), serum creatinine (sCr) and serum sodium as markers of CD, before and after initiating MET.

METHODS

Retrospective (observational) study with three cohorts:
1) patients receiving RIF then switched to MET at the end of a special access program (SAP);
2) patients started de-novo on MET at the end of the SAP; and
3) patients who received RIF as a part of the SAP and continued on it.

Demographics, clinical and laboratory parameters were collected. Analyses included: medians with IQRs; proportions; percentages; repeated measures ANOVA; ANCOVA.

RESULTS

Preliminary analysis conducted on 31 patients. See Table 1.0 for index date demographics.

HE: three episodes in 2 patients in cohorts 1) and 2) during the 6 months post-MET initiation; three episodes in 3 patients in cohort 3) during the 6 months post-RIF initiation. This is comparable to trials documenting breakthrough HE while on RIF for HE prevention.

No reported adverse effects from MET or RIF.

A decrease in sCr and increase in MAP was observed in patients treated with MET. Statistical significance was not achieved.

Back to Previous Page

CONCLUSIONS

Despite the study’s sample size and exploratory nature, it appears MET might be comparable to RIF in preventing HE and may improve markers of CD. Next steps: increasing sample size; missing values analysis; and imputation for multivariate analysis and informing larger studies.

Supervisor: Dr. Juan G. Abraldes

Back to Previous Page

Table 1.0: Demographics at Antibiotic Index Date

Age (at start of therapy with Rifaximin or Metronidazole)*	
Median Age (yrs) [IQR]	58.0 [50.0 – 63.0]
Gender	
Male	18/31 (58.1%)
Cohort	
Metronidazole after Rifaximin	5/31 (16.1%)
De Novo Metronidazole	14/31 (45.2%)
Continued Rifaximin	12/31 (38.7%)
Etiology of Cirrhosis	
Alcohol	11/31 (35.5%)
HCV	8/31 (25.8%)
Alcohol + HCV	4/31 (12.9%)
Patients with Decompensation	
Yes	31/31 (100.0%)
Type of Decompensation	
Encephalopathy	31/31 (100.0%)
Ascites	25/31 (80.6%)
Edema	17/31 (54.8%)
Variceal Bleeding	9/31 (29.0%)
Other Complications	
HCC	5/31 (16.1%)
PVT	6/31 (19.4%)
TIPS	7/31 (22.6%)
Pre-antibiotics	5/7 (71.4%)
Post-antibiotics	1/7 (14.3%)
Unknown	1/7 (14.3%)
Child Pugh Score (at start of therapy with Rifaximin or Metronidazole)*	
Median Score [IQR]	7.0 [6.0 – 8.5]
Child Pugh A	10/27 (37.0%)
Child Pugh B	12/27 (44.4%)
Child Pugh C	5/27 (18.5%)
MELD Score (at start of therapy with Rifaximin or Metronidazole)**	
Median Score [IQR]	13.0 [10.0 – 17.0]

Back to Previous Page

Using Infliximab Trough Levels and Fecal Calprotectin Levels Together to Guide Clinical Decisions has the Potential to Improve Outcomes in Inflammatory Bowel Disease Patients on Maintenance Infliximab Therapy.

Amin, Aditi; Prosser, Connie; Kroeker, Karen; Wang, Haili; Shalapay, Carol; Dhami, Neil; Fedorak, Darryl; Halloran, Brendan P.; Dieleman, Levinus; Goodman, Karen; Fedorak, Richard N.; Huang, Vivian.
Supervisor: Dr. Vivian Huang

INTRODUCTION

Infliximab (IFX) induces and maintains remission in inflammatory bowel disease (IBD). Up to 60% of patients on maintenance IFX develop secondary loss of response (LOR). Studies recommend IFX trough levels (ITLs) be maintained up to 10µg/mL to prevent LOR. However, patients have LOR despite adequate ITLs. This is due to inflammation. Fecal Calprotectin (FCP) is a marker of neutrophilic infiltration into the GI tract. Elevated FCP predicts LOR to maintenance IFX. We previously showed clinicians would change their decisions based on ITLs and FCP levels.

Aims: identify 6 month clinical outcomes in IBD outpatients on maintenance IFX; explore whether 6 month outcomes could be improved if clinicians had knowledge of both ITLs and FCP levels.

METHODS

Adult IBD outpatients on maintenance IFX had disease scores, ITLs and FCP levels measured. Initial clinical decisions were made. An expert clinician panel made hypothetical decisions with clinical data, ITLs and FCP levels. 6 month outcomes were recorded. Analyses included: medians with IQRs; proportions; percentages; and contingency tables.

RESULTS

Preliminary analysis was performed on 31 outpatients on maintenance IFX.

Demographics: median age 40.0 (IQR 29.0-59.0); 21 (67.7%) females; 23 (74.2%) with Crohn’s; 14 (45.2%) in clinical remission; and 23 (74.2%) on concomitant immunosuppresion. Median ITL 9.4 (IQR 5.4 – 16.1). Median FCP level 97.0 (IQR 14.0 – 362.0).
Table 1: the initial decision differed from the hypothetical decision in 26/31 (83.9%) of cases (blue). 6 month outcomes that related to discrepant decisions occurred in 5/31 (16.1%) of cases (red).

Further analysis: 28 patients had expert panel decisions. These decisions differed from the initial clinical decision in 16/28 (57.1%) of cases. In 4/16 (25.0%) of these cases, outcomes could have potentially been prevented using levels.

CONCLUSIONS

Back to Previous Page

Preliminary results from this study demonstrate that knowledge of ITLs and FCP levels together aids clinician optimization of IBD outpatients on maintenance IFX. This can help improve patient outcomes.

Supervisor: Dr. Vivian Huang

Antiretroviral therapy efficacy in the brain: a unique HIV-1 reservoir

Eugene L. Asahchop, Wing F Chan, William G Branton, Gail Rauw, Glen B. Baker and Christopher Power
Supervisor: Dr Christopher Power

INTRODUCTION

To cure HIV/AIDS, it is imperative to eradicate all viral reservoirs including the brain. The relative susceptibility of the HIV-1 brain reservoir (microglia and perivascular macrophages) to antiretroviral therapy (ART) is unknown. We investigated ART efficacy in HIV-infected myeloid cells together with measuring in vitro and in vivo ART concentrations.

METHODS

Human fetal microglia (HFMs), bone marrow derived macrophages (BMDMs) and peripheral blood mononuclear cells (PBMCs) were infected with HIV-1YU-2 at a multiplicity of infection (MOI) 0.1-1.0. HIV-infected cells were treated with zidovudine (AZT), etravirine (ETR), raltegravir (RAL), darunavir (DRV) or maraviroc (MVC). The EC50 levels were determined at day 4 or 5 post-infection by p24 ELISA. HPLC MS was used to ascertain the ART extracellular and intracellular concentrations in differentiated human THP-1 cells, and in mice.

RESULTS

Treatment of HIV-infected HFMs and BMDMs revealed that the EC50 (day 5 post-infection) were: AZT (93.2±20 and 56.4±10.6 nM), RAL (7.4±2.4 and 3.9±0.9 nM), MVC (1.9±0.7 and 1.6 nM), DRV (13.6 and 3.5±1.0 nM), and ETR (12.1±4.0 and 2.0±0.6 nM) respectively. The EC50 levels for AZT, RAL, MVC, DRV and ETR in PBMCs at day 4 post-infection were: 8.6±1.6, 2.3±0.4, 4.9±0.63, 1.9±0.4 and 1.3±0.1 nM respectively. In vivo concentration of RAL or DRV in mice was 25-30 fold lower in the brain compared to blood at 1 hr post-injection. Both drugs were undetectable in brain and peripheral blood at 8 and 24 hr post injection, respectively.

CONCLUSIONS

EC50 values for AZT, ETR and DRV in HIV-infected HFMs were substantially higher than those observed in PBMCs. The concentrations of RAL and DRV in brain were relatively lower compared to concentrations in blood. These results underscore consideration of assessing ART concentrations in different viral reservoirs in efforts to eradicate HIV-1.

Supervisor: Dr Christopher Power

Back to Previous Page

The effect of resveratrol-enhanced fecal transplant as a treatment for hypertension.

Suresh Bairwa, Nirmal Parajuli, Nobutoshi Matsumura, Jason Dyck
Supervisor: Dyck Jason

INTRODUCTION

Resveratrol is a bioactive phenol found in some plant-based food sources and has been used as a nutraceutical for the treatment of hypertension. We have recently shown that resveratrol ingestion induces taxonomic and functional changes of the gut microbiota and that these changes in the gut microbiota are an integral mechanism by which resveratrol exerts its beneficial effects in the treatment of hypertension. Therefore, we hypothesised that fecal material transfer (FMT) from healthy resveratrol-fed donor mice would be sufficient to treat hypertension in mice.

METHODS

8-week old C57BL/6 mice were subcutaneously implanted with Alzet micro-osmotic pump to deliver saline or Ang II (1.4mg/kg/day) for 2 weeks. These mice also received 3 FMT over a one-week period from either healthy control chow fed or healthy resveratrol fed donor mice. Mice were subjected to serial blood pressure measurement by tail-cuff pre and post-implant of micro-osmotic pumps. At the end, echocardiography was performed to assess heart function and mice were then euthanized for tissue collection.

RESULTS

At first week, Ang II treated mice that underwent FMT from chow fed diet (Ang II + Chow FMT) had significant elevated systolic blood pressure (SBP) compared with saline control (Saline + Chow FMT) ($p<0.05$). Remarkably, at the second week, Ang II treated mice that received FMT from resveratrol fed donor mice (Ang II + Resv FMT) displayed a significant reduction in blood pressure compared to Ang II + Chow FMT group ($p<0.05$). In addition, heart weight to tibia length ratios were also significantly decreased in the Ang II + Resv FMT mice compared to the Ang II + Chow FMT group ($p<0.05$).

CONCLUSIONS

Our results show that SBP is increased by Ang II and this effect is prevented by FMT from healthy resveratrol-fed donor mice. Further tissue analysis is required to understand the underlying signaling mechanism for this FMT-mediated antihypertensive activity of resveratrol.

Supervisor: Dr. Dyck Jason

Back to Previous Page

Study of Natural Health Product Adverse Reactions in Cancer Patients: Preliminary Data in Adult Patients

M. Basiuk, S. Desai, P. Venner, A. Joy, K. Tonkin, L. Zorzela, S. Vohra
Supervisor: Dr. Sunita Vohra

INTRODUCTION

According to the Canadian Cancer Society, 2 in 5 Canadians will be diagnosed with cancer in their lifetime. It is known that patients who take Natural Health Products (NHPs) are at risk for adverse events (AEs) and NHP-prescription drug interactions. Based on disease progression, prognosis and the use of narrow therapeutic index medications, cancer patients are potentially vulnerable to AEs and drug interactions. Canadian health agencies currently rely on spontaneous reports which are known to be limited by under-reporting. We are undertaking an active surveillance study in cancer clinics to identify NHP or concurrent NHP-prescription drug use and any undesirable effects associated with each.

METHODS

Using a one page screening form, clinic staff asked their patients about prescription drugs and NHP use in the last month. Patients were asked about any undesirable effects and what actions, if any, were taken to treat them. Clinicians were also prompted to report AEs they had observed.

RESULTS

This study is in the initial stage of data collection. Locally, at the Cross Cancer Institute we have screened a total of 392 adult patients. Of those patients, 32.1% (126) take prescription medications alone, 9.2% (36) take NHPs alone, 45.9% (180) take both concurrently and 12.8% (50) take neither. In terms of incidence of AE, 50.8% reported an AE while taking prescription medications alone, 5.6% with use of NHPs alone, 38.3% with the combination of NHP and prescription medication use and 24% with the use of neither.

CONCLUSIONS

We were able to successfully initiate the process of screening for NHPs and potential AEs at a local cancer clinic and are beginning data collection at conventional and integrative sites in other cities of Alberta, Ontario and British Columbia. The majority of cancer patients are taking NHPs and a large proportion are using NHPs along with prescription medication.

Supervisor: Dr. Sunita Vohra

Back to Previous Page

Optimization of IVIG Treatment for Neuromuscular Patients in Rural Areas of Northern Alberta

Derrick Blackmore BSc, Zaeem Siddiqi MD PhD
Supervisor: Zaeem Siddiqi MD PhD

INTRODUCTION

Most routine intravenous immunoglobulin (IVIg) infusions prescribed for neuromuscular patients in Northern Alberta are administered in urban hospitals in Edmonton. This inaccessibility to IVIg results in rural regions leads to delay in treatment and potential worsening of the disease, travel costs to the patients, and lost work days. This study assessed the feasibility and safety of providing IVIg infusions at rural facilities closer to the point of need.

METHODS

A prospective observational study was conducted. Neuromuscular patients and infusion room nurses at rural and urban centers recorded their IVIg infusion experiences and associated adverse effects. We compared data for rural/urban access; differences in safety, and patients' and infusion room nurses' experience were identified. Costs were calculated for both cohorts and compared to an economic model.

RESULTS

The mean wait time for rural centres was 7.05 (±0.84) days while for urban centers in Edmonton for 13.5 (±8 days). Regression analysis illustrated a positive correlation between wait times and regional population (p=.002). Safety measures were similar between rural and urban patients; both infusion staff and patients reported similar incidence of adverse events (AE's) at both locations (21% urban vs. 25% rural). Reported AE's were mild, headache being the most common. Patient and staff satisfaction scores were high, averaging >90% for a treatment timeliness, comfort and knowledge. Infusion costs at urban and rural sites were nearly identical at approximately $62.00 for a full 5-day course. By contrast, economic modelling demonstrated significant financial burdens on rural patients of approximately $80.00-$1000.00 depending on the distance from Edmonton.

CONCLUSIONS

IVIg infusions within rural settings are safe and feasible, resulting in improved wait times and reduced costs for patients. Academic centers should have programs to make this potentially lifesaving therapy more accessible to rural regions.

Supervisor: Dr. Zaeem Siddiqi MD PhD

Back to Previous Page

Outcomes in CKD patients with hospital acquired complications

Babak Bohlouli1, Terri Jackson2, Marcello Tonelli1, Scott Klarenbach1
Supervisor: Scott Klarenbach

INTRODUCTION

Patients with CKD are at increased risk of hospital acquired complications (HACs) including those considered preventable. The impact of HACs on patient and health system outcomes has not been well described.

METHODS

Subjects hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) were studied. Outpatient eGFR and proteinuria (protein/creatinine ratio or dipstick) in the year prior to index hospitalization were used to define CKD status. Co-morbid conditions were identified using validated algorithms applied to administrative data. ICD 10 CA was used to classify reason for admission. A specific diagnostic indicator (type II) was used to identify hospital acquired complications (HACs) that were sub-classified as “potentially” and “always” preventable. We studied the following outcomes: re-admission within 90 days of discharge, all cause mortality at 90 days, and index hospitalization costs. Multivariable regression models examined the association of HACs with re-admission, mortality, and incremental health care costs, accounting for confounders.

RESULTS

Of 536,549 subjects, 45,377 (8.5%) with CKD were hospitalized. In patients with HACs, the OR of re-admission and death at 90 days was 1.37 (95% CI: 1.32 – 1.43), and 3.31 (95% CI: 3.06 – 3.58) respectively compared with those without HAC. Hospitalizations with any HAC were associated with median incremental health costs of $4028 (95% CI: $3898 – $4158). A graded association was observed for those outcomes with increasing number of HACs and severity of CKD. Similar results were noted when only potentially preventable HACs were considered.

CONCLUSIONS

Complications occurring during hospitalization in patients with CKD is independently associated with an increased risk of hospital re-admission, health care costs, and mortality. Targeted strategies to reduce HACs in this patient population may have a significant benefit.

Supervisor: Dr. Scott Klarenbach

Back to Previous Page

Health care costs of hospital acquired complications in patients with CKD

Babak Bohlouli1, Terri Jackson2, Brenda Hemmelgarn3, Marcello Tonelli3, Scott Klarenbach1
Supervisor: Scott Klarenbach

INTRODUCTION

Patients with CKD are vulnerable to hospital acquired complications (HACs), including those considered preventable. Understanding the economic burden of HACs can define the scope of strategies aimed at preventing complications and their consequences.

METHODS

Subjects hospitalized from April 1, 2003 to March 31, 2008 from a population based cohort (Alberta Kidney Disease Network) were studied. KDIGO criteria were used to categorize CKD using serum creatinine and urine protein. Type II diagnostic flag and published literature were used to identify “all”, “potentially” and “always preventable” complications using hospital discharge information. Index hospitalization and readmission costs were determined using CIHI CMG methodology; physician claims and ambulatory care costs were also determined. The total cost of the index hospitalization, and within 90 days after discharge were determined. Purposeful multivariable regression, Tobit, and quantile models (where appropriate) estimated the incremental health care costs associated with preventable complications; generalized linear model was used for sensitivity analysis.

RESULTS

Of 45,336 subjects, 4,441 (9.80%) had ≥ 1 preventable complication, associated with median incremental cost of $8,435 (95% CI: 8,184 – 8,686). A graded association was observed for incremental cost with increasing number of preventable complications. The association of HAC and increased costs persisted when patients were subdivided into length of stay quartiles; e.g. the incremental cost of ≥ 1 preventable complication in the 0 - 25% quantile (≤3 days LOS) was $2,344 (95% CI: 1,976 – 2711). The 90 days post discharge incremental costs of readmission and ambulatory care was $1,429 (95% CI: 1,150 – 1,709) and $67 (95% CI: 48 – 87), respectively. Similar results were noted when all, and always preventable HACs were considered. No graded association by severity of CKD was observed.

CONCLUSIONS

Potentially preventable HACs are associated with significant increases in healthcare costs during the index hospitalization and after discharge. Targeted strategies to reduce preventable HACs may attenuate these costs.

Supervisor: Dr. Scott Klarenbach

Back to Previous Page

The Pyruvate Dehydrogenase Kinase Inhibitor Dichloroacetate enhances the antitumor activity of the Tyrosine Kinase Inhibitor Sunitinib in clear-cell renal cell carcinoma in vivo.

BOUKOURIS A, KINNAIRD A, SUTENDRA G, GURTU V, HAROMY A, MICHELAKIS ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Clear-cell renal cell carcinoma (ccRCC) exhibits suppressed mitochondrial function and profound vascularity. The mitochondrial suppression is mainly caused by phosphorylation and inactivation of pyruvate dehydrogenase (PDH) by pyruvate dehydrogenase kinase (PDK), and contributes to HIF-driven angiogenesis. PDH is also phosphorylated by upstream receptor tyrosine kinases (RTKs), which are activated in ccRCC. We hypothesized that the combination of the PDK inhibitor Dichloroacetate (DCA) and the RTK inhibitor Sunitinib would enhance Sunitinib's described antitumor effects through prevention of PDH phosphorylation, mitochondrial activation and enhanced inhibition of angiogenesis.

METHODS

786-O ccRCC cells were subcutaneously injected into the flanks of 6-weeks old nu/nu mice. Mice bearing xenografts were treated with Sunitinib alone, Sunitinib+DCA or vehicle for 14 days. Changes in tumor volumes were recorded during treatment and tumor weights were measured post-euthanasia. To measure tumor vascularity, animals were injected before euthanasia with lectin, staining perfused vessels. Tumor respiration was measured with a Seahorse Analyzer immediately post-euthanasia. Levels of phosphorylated PDH [at the tyrosine301 (RTK-driven) and the serine293 (PDK-driven) site] were assessed by immunoblots.

RESULTS

Sunitinib+DCA significantly decreased tumor volumes/weights and vascularity, more than Sunitinib alone. Vascularity (lectin fluorescence) was quantified in confocal images stacks (3D reconstruction) of the tumor. PDH phosphorylation at both sites was significantly decreased with Sunitinib+DCA compared to Sunitinib alone. While this PDH activation predicts increased respiration in isolated ccRCC cells, both treatments inhibited overall respiration in the whole tumor, a result of the hypoxia caused by decreased vascularity in vivo.

CONCLUSIONS

DCA enhanced the antitumor activity of Sunitinib in RCC by significantly increasing its anti-angiogenesis effects. Although Sunitinib is approved for use in RCC, its anti-angiogenesis effects are thought to be short-lived, explaining its minimal effects on survival. The combination with DCA (which also has primary anti-RCC effects; European Urology 2016) needs to be tested clinically.

Supervisor: Dr. Evangelos Michelakis

Back to Previous Page

PI3Kβ has distinct role in endothelial cells and cardiomyocytes facing myocardial infarction

Xueyi Chen, Jessica DesAulniers, Xiuhua Wang, Zamaneh Kassiri and Gavin Y. OuditXueyi Chen, Jessica DesAulniers, Xiuhua Wang, Allan G. Murray, Zamaneh Kassiri and Gavin Y. Oudit
Supervisor: Dr. Gavin Oudit

INTRODUCTION

The cardiomyocyte-endothelial cell crosstalk plays an important role in myocardial infarction (MI). And there has a knowledge gap in the function of PI3Kβ in the heart, which is an isoform of class IA PI3K and involves in the activation of pro-survival PI3K/Akt pathway. Here we aim to test the function of PI3Kβ in endothelial cells and cardiomyocytes following MI.

METHODS

Mice with kinase-dead p110β (the catalytic subunit of PI3Kβ) expressed specifically in cardiomyocyte (p110βCre) or endothelial cell (p110βMer) were generated, and littermates (p110βFlx) were used as control. Intraperitoneal injection with tamoxifen was given to 9/10-week-old p110βMer mice to activate endothelial-specific gene deletion. Sham-operation or MI-surgery on 12-week-old mice and echocardiography after 7 days were performed in a blinded fashion. Mortality data were collected. TTC, CD31, and WGA staining were performed to test the infarct size, vascular density, and cardiomyocyte size on 7-day post-operated mice. Signaling pathways were assessed by Western blot.

RESULTS

PI3Kβ was present in the cardiac microvasculature at baseline, while post-MI setting caused relocalization of PI3Kβ to the membrane of cardiomyocyte in the peri-infarct area examined via p110β staining. In sham groups, three genotypes showed comparable data on cardiac function, vascular density, and cardiomyocyte size. However, on 7-day post-MI groups, p110βMer showed improved systolic function compared to p110βFlx, while p110βCre had deteriorated systolic function along with greater hypertrophy and lower vascular density in the non-infarct area. 7-day post-MI p110βMer hearts showed smaller infarct size and higher vascular density in peri-infarct and infarct areas, while cardiomyocyte size was similar. An increase of pAkt and pErk1/2 were present on 7-day post-MI hearts in p110βMer group.

CONCLUSIONS

Protection from MI in p110βMer hearts might be due to an over-activation of PI3Kα regulated by feedback mechanism, up-regulating the angiogenic PI3K/Akt pathway. Cardiomyocyte PI3Kβ might be important in maintaining cardiac function after MI, probably via suppression of cardiomyocyte death.

Supervisor: Dr. Gavin Oudit

Back to Previous Page

Social Cognition and Executive Functions in Amyotrophic Lateral Sclerosis

Sneha Chenji, Dennell Mah, Wendy Johnston, Sanjay Kalra
Supervisor: Sanjay Kalra

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative condition characterized by muscular weakness due to the loss of motor neurons. Additionally, studies report changes in executive functions (EF), language, social cognition (ability to perceive, understand and respond to social stimuli) and behaviour (apathy and disinhibition) due to frontotemporal lobar degeneration (FTLD) observed in a proportion of patients. While, there is an appreciation for the presence of social cognition deficits, the prevalence of these deficits and the impact of EF on social cognition are yet to be established.

METHODS

We recruited 32 ALS patients and 31 age-education matched healthy volunteers. Reading the Mind the Eyes (RME) test, the Faux pas test and Judgement of Preference test (from the Edinburgh ALS Cognitive and Behavioural Screen, ECAS) were administered to measure social cognition. Additionally, an extensive neuropsychometric battery assessing executive functions, language, learning and visuospatial abilities was also administered. Percent of ALS patients impaired (<-2SD), independent samples t-test and Pearson correlations were analyzed for significance at $p<0.05$.

RESULTS

Our results show that a higher proportion of patients (13%) are impaired in faux pas detection - a measure of social cognition, followed by empathy (10%), understanding intentions (10%) and beliefs (7%). While patients were impaired on a single domain of either EF or social cognition, patients were not impaired simultaneously on both domains. Correlations indicated that lower executive function scores significantly correlated with poor performance on social cognition tasks. No significant group differences were found in performance on neuropsychometric tests between the patient and the control groups.

CONCLUSIONS

Our findings are supportive of previous literature indicating prevalence of social cognition impairments in ALS patients. While deficits in social cognition and EF did not co-exist in our sample, significant correlations between these cognitive domains indicate that executive functions may play a role in contributing to social cognition deficits.

Supervisor: Dr. Sanjay Kalra

Back to Previous Page

Gastroenterology curriculum in the Canadian medical school system

ThucNhi Tran Dang, Clarence Wong, and Lana Bistritz
Supervisor: Dr. Lana Bistritz

INTRODUCTION

Gastroenterology is a diverse subspecialty that covers a wide array of topics ranging from functional abdominal pain to gastrointestinal (GI) malignancies. The pre-clinical GI curriculum is often the only formal training that medical students receive prior to becoming residents and where fundamental knowledge of GI diseases are developed. Despite this, there is no national consensus or awareness on content, learning objectives, or instructional methods for the GI curriculum at other Canadian institutions.

METHODS

A survey of GI teaching topics, teaching methods, and assessment tools was developed by two educational content experts involved in organizing the GI curriculum at the University of Alberta. This survey was piloted internally to two additional gastroenterologists and to two external gastroenterologists involved in organizing the GI curriculum for review. The final questionnaire was sent to all the GI pre-clinical curriculum coordinators at all 17 Canadian medical schools in the October 2014.

RESULTS

A total of 10 of 17 schools completed the questionnaire. A curriculum map of GI topics showed a heterogenous curriculum across the country. Surgical topics (i.e. abdominal trauma, anorectal pain, fecal incontinence, gastrointestinal tumours, hernias, and obesity/bariatric surgery), food allergies and intolerances, pediatric constipation and diarrhea were taught at half or less than half of the medical institutions. The curriculum was taught primarily by gastroenterologists and surgeons. Lectures and small group teaching were the most common teaching methods employed and Liver Diseases employed the most diverse teaching methods.

CONCLUSIONS

This is the first study examining the GI curriculum at a pre-clinical level. The data from this study can be used to reform curriculum such that topics which are generally lacking are better incorporated in the curriculum and can be used as a guide in further curriculum design.

Supervisor: Dr. Lana Bistritz

Back to Previous Page

	A	B	C	D	E	F	G	H	I	J
Pediatric Abdominal Pain	■		■		■	■	■	■	■	
Abdominal Trauma			■		■				■	■
Abnormal Liver Enzymes	■	■	■	■	■	■	■	■	■	■
Acetomenophen Toxicity	■	■			■	■	■	■		■
Acute Abdomen / Abdominal Pain	■		■	■	■	■	■	■	■	■
Acute Diarrhea	■	■	■	■	■	■	■	■	■	■
Adult Constipation	■	■	■	■	■	■	■	■	■	■
Ano-rectal Diseases	■	■	■	■	■	■	■		■	■
Anorectal Pain	■		■			■			■	
Appendicitis	■		■	■	■		■	■	■	■
Ascites	■	■	■	■	■	■	■	■	■	■
Bowel Cancer	■	■	■	■	■	■	■	■	■	■
Bowel Dilation / Obstruction	■	■	■	■	■		■	■	■	■
Celiac Disease	■		■	■	■	■	■	■	■	■
Chronic Abdominal Pain	■		■		■	■	■	■	■	■
Chronic Diarrhea	■	■	■	■	■	■	■	■	■	■
Diverticular Disease	■	■	■		■	■	■	■	■	■
Dysphagia	■	■	■		■	■	■	■	■	■
Esophageal Cancer	■	■	■		■	■	■	■	■	■
Motility Disorders	■	■	■		■	■	■	■	■	■
Fecal Incontinence	■		■			■		■	■	
Food Allergy / Intolerance	■				■		■			
Gallstones	■		■	■	■	■	■	■	■	■
Gastric Cancer	■	■	■	■	■	■	■	■	■	
Gastrointestinal Tumours	■	■	■		■				■	
GERD	■	■	■	■	■	■	■	■	■	■
Hepatomegaly / Hepatology	■	■	■	■	■		■	■	■	■
Hernias	■		■		■			■	■	
Inflammatory Bowel Disease	■	■	■	■	■	■	■	■	■	■
Irritable Bowel Syndrome	■	■	■	■	■	■	■	■	■	■
Jaundice	■	■	■	■	■	■	■	■	■	■
Liver Cancer	■	■	■		■	■	■	■	■	
Lower GI Bleed	■	■	■	■	■	■	■	■	■	■
Malabsoprtion	■		■	■	■	■	■	■	■	■
Metabolic Liver Disease	■	■	■		■	■	■	■	■	■
Nausea / Vomiting	■		■		■	■	■	■	■	■
Nutritional Support	■		■	■	■		■		■	■
Obesity / Bariatric Surgery	■						■		■	■
Pancreatic Cancer	■	■	■		■		■	■	■	
Pancreatitis	■	■	■	■	■	■	■	■	■	■
Pediatric Constipation	■		■			■	■			
Pediatric Diarrhea	■	■	■			■	■		■	
Peptic Ulcer Disease	■	■	■	■	■	■	■	■	■	■
Splenomegaly	■	■			■		■		■	■
Upper GI Bleeding	■	■	■	■	■	■	■	■	■	■
Viral Hepatitis	■	■	■		■	■	■	■	■	■

Back to Previous Page

Outcomes of Transfusions in Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: A Population Level Analysis

Authors: Sumandeep Dhesi S, MD; Danielle A. Southern, MSc; Matthew T. James, MD PhD; Michelle M. Graham, MD
Supervisor: Dr. Michelle M. Graham

INTRODUCTION

Anemia is present in up to 20% of patients hospitalized with coronary heart disease. Both anemia itself and transfusions are associated with adverse clinical outcomes. Transfusion triggers for acute coronary syndromes (ACS), including those managed with percutaneous coronary intervention (PCI), are not well defined. We sought to: (1) characterize transfusion patterns for ACS patients undergoing PCI in Alberta (AB); and (2) determine whether transfusions are associated with worsened clinical outcomes.

METHODS

Registry data from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) was linked to administrative data from Alberta Health and to Vital Statistics, providing clinical, laboratory, and outcomes information on all patients with ACS undergoing PCI from 2009 to 2014.

RESULTS

Laboratory data was available on 4,121 ACS patients undergoing PCI, and 1% (n = 165) of PCI patients received red blood cell transfusion. Patients receiving transfusion were more likely to be older, have chronic medical conditions, and have complex coronary anatomy (Table 1). The mean nadir hemoglobin (Hgb) value associated with transfusion was 93 g/L. The majority of transfusions occurred with Hgb values >70 g/L (95%). Transfusion was associated with increased 30 day (OR 8.7, 95% CI 4.1-18.2) and 1-year mortality (OR 5.3, 95% CI 2.8-9.9) in adjusted analysis.

CONCLUSIONS

Our study highlights the use of a liberal transfusion strategy in patients with ACS undergoing PCI in Alberta. Transfusions were independently associated with higher mortality at up to 1 year of follow up.

Supervisor: Dr. Michelle M. Graham

Back to Previous Page

Table 1. Characteristics of ACS patients undergoing PCI.

Characteristics	Not transfused n=3,956	Transfused n=165	p-value
Age ≥75 years	751 (19.0%)	63 (38.2%)	<0.0001
Male	2,955 (74.7%)	101 (61.2%)	0.0001
Comorbidities			
Dialysis	22 (0.6%)	26 (15.8%)	<0.0001
Diabetes	1,018 (25.7%)	81 (49.1%)	<0.0001
Malignancy	138 (3.5%)	14 (8.5%)	0.0008
Prior CABG	207 (5.2%)	15 (9.1%)	0.032
Prior PCI	482 (12.2%)	28 (17.0%)	0.067
Prior MI	623 (15.8%)	52 (31.5%)	<0.0001
Liver/GI disease	276 (7.0%)	29 (17.6%)	<0.0001
Cerebrovascular Disease	163 (4.1%)	24 (14.6%)	<0.0001
Peripheral Vascular Disease	588 (14.9%)	28 (17.0%)	0.457
Pulmonary Disease	508 (12.8%)	49 (29.7%)	<0.0001
Renal Disease	159 (4.0%)	54 (32.7%)	<0.0001
HF	266 (6.7%)	60 (36.4%)	<0.0001
Current Smoker	1,417 (35.8%)	37 (22.4%)	0.0004
Hypertension	2,796 (70.7%)	133 (80.6%)	0.006
Hyperlipidemia	2,865 (72.4%)	122 (73.9%)	0.670
PCI Characteristics			
DES	2,043 (51.6%)	62 (37.6%)	0.0004
Emergency PCI	378 (9.6%)	23 (13.9%)	0.063
Duke Coronary			<0.0001
Low Risk	2,098 (53.0%)	77 (46.8%)	
High Risk	695 (17.6%)	52 (31.5%)	
Left Main	88 (2.2%)	14 (8.5%)	
Laboratory Data			
Mean Hgb* (s.d.)	137.71 (17.05)	93.17 (22.73)	<0.0001
Hgb Range			<0.0001
≤50	1 (0.03%)	1 (0.6%)	
51-70	2 (0.05%)	7 (4.2%)	
71-90	49 (1.2%)	94 (57.0%)	
91-110	213 (5.4%)	32 (19.4%)	
111-130	718 (18.2%)	12 (7.3%)	
Normal	2,973 (75.2%)	19 (11.5%)	

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; GI, gastrointestinal; HF, heart failure; DES, drug-eluting stent; Hgb, hemoglobin.
*All Hgb levels measured in g/L.

Back to Previous Page

INDEPENDENT PREDICTORS OF FAILURE OF FECAL MICROBIOTA TRANSPLANTATION (FMT) FOR RECURRENT OR REFRACTORY CLOSTRIDIUM DIFFICILE INFECTION

Joseph Dimitry, Ammar Keshteli, Dina Kao
Supervisor: Dr Dina Kao

INTRODUCTION

Fecal microbiota transplantation (FMT) is a safe and effective alternative therapy for treatment of refractory or recurrent C. diff infection (RCDI), with an overall success rate of 80-90% with one treatment. However, it is unknown which patients will require more than one FMT or who will not respond to FMT. Our goal was to identify clinical predictors of treatment failure following a single FMT in recurrent or refractory disease.

METHODS

This retrospective study included 136 patients who received FMT for refractory or recurrent CDI at the University of Alberta hospital. Patient baseline characteristics and clinical datasets were abstracted from in-patient charts and electronic medical records.

RESULTS

Of the 136 patients, 106 (77.9%) were cured following one FMT. Univariate analysis identified 7 factors, shown in Table 1, associated with failure of 1 FMT. Multivariate analysis revealed that inpatient status (OR 7.4; 95% CI 2.2-24.6, p=0.001), immunosuppression (OR 4.5; 95% CI 1.3-16.2, p=0.020), and severe or complicated CDI (OR 5.2; 95% CI 1.2-21.6, p=0.025) were factors most independently associated with failure following 1 FMT. All 9 refractory patients failed the 1st FMT. Of the 30 patients (22.1%) who failed the first FMT, 25 received a second and 16 were cured.

CONCLUSIONS

Inpatient status, immunosuppression, and severe or complicated disease are independent predictors of treatment failure following 1 FMT in RCDI patients. Clinicians can predict patients most at risk of treatment failure and adjust treatment and discharge planning accordingly.

Supervisor: Dr Dina Kao

Back to Previous Page

Characteristic	Success n=106	Failed n=30	p-value
Age	67.0 (17.4-97.7)[1]	74.3 (23.1-88.4)	0.354
Women	64 (60.4%)	14 (46.7%)	0.180
Immunosuppressed	21 (19.8%)	11 (36.7%)	0.055
Chronic PPI[4]	50 (47.2%)	19 (63.3%)	0.118
Post FMT ABX[5]	16 (15.1%)	7 (23.3%)	0.288
Chronic Statin[4]	35 (33%)	14 (46.7%)	0.169
IBD	13 (12.3%)	2 (6.7%)	0.388
Charlson Index	13 (12.3%)	5 (0-11)	0.013
COPD[2]	4 (0-11)	10 (33.3%)	0.007
Maximum WBC[6]	13.4 (4.7-45.4)	21.1 (6.7-58.3)	<0.001
Hospital-acquired	36 (34%)	21 (70%)	<0.001
Inpatient Status	19 (17.9%)	21 (70%)	<0.001
Refractory to ABX[3]	0	9 (30%)	<0.001
Severe/Complicated	6 (5.7%)	11 (36.7%)	<0.001

Back to Previous Page

Assessing Sleep Quality in Patients with Inflammatory Bowel Disease Reporting Fatigue

Alexandra E. Dittrich (1, 2, 5), Karen Goodman (1, 2, 3), Brian McNab (2, 4), Karen I. Kroeker (1, 2, 5)
Supervisor: Dr. Karen I. Kroeker

INTRODUCTION

Inflammatory bowel disease (IBD), a non-curable inflammatory condition, can affect any part of the gastrointestinal tract. Symptoms include diarrhea, nocturnal bowel movements, rectal bleeding, and abdominal pain. Nevertheless, even when gastrointestinal symptoms are in complete remission, fatigue remains a symptom and negatively impacts quality of life for many patients.
Recently we examined the prevalence of fatigue in our population of IBD patients and identified 53.7% of patients with IBD having severe fatigue. In this same study, 41.9% of patients reported negative changes in sleep. Though sleep disturbance and fatigue may be aggravated by disease activity, they have been shown to be significant even when the disease was in remission.

METHODS

A literature review was done to identify studies addressing sleep disturbance, fatigue, and factors influencing sleep disturbance including medications, sleep-related disorders, and depression in patients with IBD.

RESULTS

Few studies have addressed sleep disturbance in the IBD population. These studies have highlighted that sleep disturbance in IBD can lead to adverse effects including daytime impairment, disease activity, and decreased quality of life. Few researchers have used objective measurements to analyze the architecture of sleep in patients with IBD. The relationship between fatigue and sleep disturbance has not been studied using both objective and subjective tools to measure sleep.

CONCLUSIONS

Fatigue remains to be a common complaint in patients with IBD in remission. Though other chronic diseases have looked at sleep disturbance, such as rheumatoid arthritis, little research has been done to specifically analyze the relationship between fatigue and sleep disturbance in IBD. It is evident that sleep disturbance can create adverse health problems if not treated, thus, it is important to identify and treat.

We have created a pilot study to understand the relationship between fatigue and sleep disturbance in our IBD population via the use of validated questionnaires and polysomnographic tools.

Supervisor: Dr. Karen I. Kroeker

Back to Previous Page

The Within-Stool and Within-Day Variability of Fecal Calprotectin in Patients with Inflammatory Bowel Disease

Lillian Du, Rae Foshaug, Vivian Huang, Karen Kroeker, Levinus Dieleman, Brendan Halloran, Karen Wong, Richard Fedorak
Supervisor: Dr. Richard Fedorak

INTRODUCTION

Fecal calprotectin (FC) is a neutrophil cytosolic protein, and its level in feces is proportional to the degree of neutrophil migration into the bowel lumen. The use of FC as stool biomarker for differentiating inflammatory bowel disease (IBD) from IBS has been well validated, and there is a strong correlation between FC and the presence of endoscopic inflammatory lesions. However, recent studies have demonstrated within-day and between-day FC variability in patients with active IBD, possibly limiting the reliability of using a single sample for monitoring disease activity and guiding management. Our aim is to assess the within-stool and within-day variability of FC concentrations in patients with Crohn's disease or ulcerative colitis.

METHODS

This is a prospective observational study evaluating a cross-sectional cohort of IBD patients 18 years or older presenting for outpatient follow-up or being admitted to hospital in clinical flare. Eligible patients were instructed to collect three stool samples from their first bowel movement of the day and from up to two additional bowel movements within 24 hours. FC concentrations were measured by a rapid, quantitative point-of-care test using lateral flow technology (Quantum Blue ®). Descriptive statistics were used to assess FC variability within a single bowel movement and between different movements. Clinically significant variability was assessed at different cut-offs for FC positivity.

RESULTS

At increasingly higher cut-offs for FC positivity, the proportion of time FC variance affected clinical outcomes decreased. The proportion of time FC variance affected clinical outcomes tended to be lowest when samples were collected in the morning.

CONCLUSIONS

There is significant variability in FC levels within a single bowel movement and between different bowel movements. Considering a single FC sample, we found that the first sample of the day with an FC positivity cut-off of 250 µg/g provided the most reliable indication of disease activity.

Supervisor: Dr. Richard Fedorak

Back to Previous Page

A Comparison of Fecal Immunochemical Testing to Guaiac-Based Fecal Occult Blood Testing in a Colon Cancer Screening Program

Lillian Du, Barbara Moysey, Amy Morse, Christopher Teshima, Richard Sultanian
Supervisor: Dr. Richard Sultanian

INTRODUCTION

Programmatic population-based colorectal cancer (CRC) screening was initiated in Edmonton in 2011 as the SCOPE program, offering colonoscopy to patients with a positive guaiac-based fecal occult blood test (gFOBT). A growing body of literature has demonstrated that the fecal immunochemical test (FIT) has improved sensitivity, without loss of specificity, for detection of advanced adenomas and CRC. Thus, at the end of 2013, FIT replaced gFOBT as the first-line CRC screening test in Alberta. The impact of the transition from gFOBT to FIT on a screening colonoscopy program has not yet been reported.

METHODS

A retrospective cohort analysis was performed of a prospectively maintained database of patients aged 50-74 who underwent colonoscopy in the SCOPE program between January 1, 2013 and December 31, 2014 as a result of a positive gFOBT or FIT.

RESULTS

649 patients underwent colonoscopy due to positive gFOBT in 2013, and 2176 patients underwent colonoscopy due to a positive FIT in 2014. The FIT group had significantly higher detection rates compared to the gFOBT group for polyps, adenomas, and advanced adenomas, but not for CRC, which was detected more frequently among gFOBT-positive patients. Multivariate regression analysis demonstrated that a positive FIT remained the strongest predictor for adenoma and advanced adenoma detection.

CONCLUSIONS

The conversion of the CRC screening program in Edmonton from gFOBT- to FIT-based selection of patients was associated with an increase in program participation, and thus the number of colonoscopies performed. Furthermore, the conversion to FIT screening resulted in significantly higher detection rates for polyps, adenomas, and advanced adenomas. While FIT produced a lower CRC detection rate, the total number of CRC cases detected by FIT was higher than by FOBT due to increased FIT utilization.

Supervisor: Dr. Richard Sultanian

Back to Previous Page

NMR Metabolomics Analysis of Urine Samples and Correlation of Creatinine Levels with Jaffe Reaction Values

Meghan Dueck, James Mino, Sindhu Nair, Marc Cassiéde, Ryan MacKay, Pascal Mercier, Bernadette Quémerais, and Paige Lacy
Supervisor: Dr. Paige Lacy

INTRODUCTION

The project objective is to measure urinary metal concentrations and metabolites to determine specific metabolite/metal profiles for a parallel study determining biomarkers of exposure to welding fumes. Optimization was initiated with control laboratory workers in a pilot project to develop a methodology for this purpose.

METHODS

Fasting urine samples (n=10) were collected from laboratory workers in June 2015. An aliquot of each sample was analyzed by ICP/MS to evaluate 12 metal concentrations. Samples were also analyzed on 600 and 700 MHz NMR spectrometers. NMR spectra were analyzed using Chenomx NMR Suite software to determine metabolite profiles. Additionally, creatinine concentrations in urine samples were determined using the Jaffe reaction by Alberta Health Services (AHS) based in the Department of Laboratory Medicine and Pathology, University of Alberta.

RESULTS

Metal concentrations in laboratory controls were similar to concentrations found in a recent study from the UK for non-exposed subjects. In total, 151 metabolites were identified and quantified by NMR in our urine samples. Creatinine concentrations in our urine samples were nearly identical for NMR spectrometers and the Jaffe reaction (CV=0.2-3.0%). We detected 59 metabolites showing strong correlations ($r2>0.7$) between 600 and 700 MHz spectrometers. Differences in metabolite concentrations were observed for another 92 metabolites ($r2<0.7$), usually due to low metabolite levels and/or spectral overlapping.

CONCLUSIONS

We found that urinary creatinine levels could be reliably measured by NMR spectroscopy with values nearly identical to that of the standardized Jaffe reaction used by the AHS clinical lab. It was determined that 39% of metabolites could be reproducibly measured between two distinct NMR spectrometers, suggesting that careful analysis and pre-screening of metabolites in quality control (QC) samples must be carried out before comparisons may be made with test groups.

Supervisor: Dr. Paige Lacy

Back to Previous Page

Manipulation of APC-β-Catenin signaling pathway promotes peripheral nerve regeneration

Arul Duraikannu, Anand Krishnan and Douglas W. Zochodne
Supervisor: Dr.Douglas Zochodne

INTRODUCTION

Peripheral nerve injures cause partial or total loss of motor, sensory and autonomic function. Unfortunately regeneration after injury is restrained without specific therapy available to facilitate it. In recent work, our laboratory exploited newer approaches to improve regrowth of damaged neurons by suppressing 'brakes' on regeneration that normally attenuate tumour growth. In the current study, we explored the potential role of the APC (adenomatous polyposis coli)-β-catenin interaction in the injury and regrowth response of adult peripheral sensory neurons.

METHODS

Adult DRG (L4-L5) sensory neurons harvested from male Sprague-Dawley rats, with previous axotomy were used for in vitro studies. qRT-PCR, Western blot and immunohistochemistry techniques were used to measure mRNA and protein levels. Dissociated neuron cultures three days after nerve injury were administered siRNA directed against APC or scrambled sequences. Neurite extension was analyzed by MetaXpress software. Regeneration was assessed by the hind paw grip strength, thermal, mechanical sensitivity and analysed electrophysiologically and morphologically.

RESULTS

Here we identified that primary sensory neurons express APC, and that peripheral nerve injury increases APC expression in DRG and sciatic nerve in vivo. The expression of APC in neurons modulates the growth signalling pathway in response to axon injury. β-catenin/LEF-TCF signalling promoted increased neurite out growth in vitro following nerve injury with APC knockdown. Inhibition of β-catenin activity reduced neurite outgrowth in vitro. Most importantly, in vivo knockdown of APC using nonviral siRNA transfection enhanced regenerating sensory and motor nerve conduction velocities, promoted functional recovery of thermal and mechanical sensitivity, and enhanced repopulation of nerves with myelinated axons.

CONCLUSIONS

Overall, our findings suggest that manipulation of the APC-β-catenin pathway promotes peripheral axon growth and represents another potential strategy for the recovery of peripheral nerve injury.

[Supported by CIHR, UHF, DoM, FoMD University of Alberta]

Supervisor: Dr.Douglas Zochodne

Back to Previous Page

Role of RIP2 in allergic airway inflammation

Yahya Fiteih, Shairaz Baksh and Harissios Vliagoftis
Supervisor: Harissios Vliagoftis

INTRODUCTION

Persistent NF-κB activation has been associated with allergic airway inflammation in asthma. Receptor interacting protein 2 (RIP2) is a serine /threonine kinase that have been implicated in NF-κB activation. Interestingly, RIP2 polymorphism has been associated with severe childhood asthma. Moreover, RIP2 gene silencing attenuated airway inflammation and airway hyperresponsiveness in ovalbumin-induced mouse asthma model. Data mentioned above indicate that RIP2 is essential for airway inflammation development, but the mechanism is not fully understood. We hypothesize that RIP2 is required for appropriate T cell response to allergens and inhibition of RIP2 will alter T cell activation and initiates a defective immune response. To further investigate the role of RIP2 in asthma we will explore the effect of inhibiting RIP2 in mouse model of asthma using a new selective inhibitor (RIP2 inhibitor-1) that was designed by Dr. Shairaz Baksh.

METHODS

Male Balb/c mice (6-8 weeks old) were sensitized with ovalbumin (10µg) + aluminium hydroxide (2mg) via intraperitoneal (i.p) injection and challenged intranasally with ovalbumin only (50µg). RIP2 inhibitor-1(1µg/g body weight) was administrated via i.p injection during the challenge phase. The mice were euthanized 24 hrs after the last challenge and bronchoalveolar lavage (BAL) fluid was collected and airway inflammation was assessed by determining total and differential cell counts in BAL fluid. Lung tissues were collected for cytokine and chemokine analysis using a 32 cytokine multiplex assay.

RESULTS

There was significant decrease in the total number of cells in BAL fluid from mice treated with RIP2 inhibitor-1(304,000 ± 91,630, n= 5) when compared to mice treated with ovalbumin only (1.6x106 ± 528,859, n= 4). Also, there was significant decrease in the percentage of eosinophils in BAL fluid from mice treated with RIP2 inhibitor-1.

CONCLUSIONS

RIP2 inhibtor-1 attenuated airway inflammation in ovalbumin-induced experimental asthma. RIP2 inhibition may be a novel therapeutic approach for the treatment of asthma.

Supervisor: Dr. Harissios Vliagoftis

Back to Previous Page

Obesity From Leptin Receptor Deficiency Provides Resistance to the Development of Pulmonary Hypertension from Monocrotaline

Vikram Gurtu, Adam Kinnaird, Spencer Proctor, Gopinath Sutendra, and Evangelos Michelakis
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a proliferative vascular disease characterized by mitochondrial suppression in the pulmonary artery and right ventricle (RV), but also other systemic tissues, similar to what is seen in metabolic syndrome and obesity. Some studies suggest that obesity may paradoxically be a protective factor in PAH, similar to what has been shown in congestive heart failure (i.e. the obesity paradox). As leptin receptor polymorphisms, hyperleptinemia, and leptin resistance are associated with obesity, we hypothesized that obese, leptin receptor deficient rats (JCR:LA-cp rats) would be protected from developing pharmacologically induced PAH by monocrotaline (MCT), a standard PAH model.

METHODS

JCR:LA-cp rats were given intraperitoneal injections of MCT (n=6) vs. vehicle (n=6) and compared to lean JCR rats (n=6 MCT and n=6 vehicle). After three weeks, hemodynamics were assessed using echocardiography and right heart catheterizations with Millar catheters.

RESULTS

Leptin receptor deficient rats were more obese than lean controls (weighing 528 ± 8g versus 343 ± 4g). In lean control rats (normal leptin receptor levels), MCT increased RV systolic pressure (RVSP) compared to vehicle (43.0 ± 3.5mmHg vs. 26.2 ± 0.7mmHg, $p<0.01$), and increased RV mass (221 ± 19mg vs. 161 ± 9mg). Furthermore, cardiac output was reduced in MCT lean rats compared to vehicle (120.8 ± 7.5µL/min vs. 84.2 ± 9.7µL/min, $p<0.05$). However in obese, leptin receptor deficient rats, MCT did not increase RVSP vs. vehicle (33.5 ± 4.1mmHg vs. 30.2 ± 1.3mmHg) or RV mass and cardiac output was unchanged.

CONCLUSIONS

Leptin receptor deficient rats are resistant to MCT induced PAH indicating that leptin downstream signaling may contribute to pulmonary vascular and RV remodeling. Impaired leptin signaling in obesity may explain the “obesity paradox” of PAH, revealing a novel pathway that could be therapeutically targeted in PAH.

Supervisor: Dr. Evangelos Michelakis

Back to Previous Page

NOVEL APPROACH FOR DIRECT ASSESSMENT OF IN VIVO RENAL SYMPATHETIC NERVE ACTIVITY IN RESPONSE TO ELEVATED RENAL VENOUS PRESSURE IN RATS

Shereen M. Hamza & Branko Braam
Supervisor: Dr. Branko Braam

INTRODUCTION

The intimate connection between cardiac and renal function is of clinical concern due to significant, poorly explained mortality in heart failure (HF) patients with diminished renal function. Increased central venous pressure in HF leads to increased renal venous pressure (RVP) which may, in turn, impair renal function. We have recently described an increase in renal vascular resistance (RVR) in response to increased RVP, which was abolished by renal denervation, suggesting a modulatory role of renal sympathetic nerves on renal hemodynamics in response to changes in RVP. In the first description of its kind, we developed and validated sophisticated surgical model by which renal sympathetic nerve activity (RSNA) can be directly measured in response to manipulation of RVP in vivo.

METHODS

Anesthetized rats were surgically instrumented with catheters to measure mean arterial pressure (MAP) and allow i.v. infusion. A sling was implanted around the left renal vein, to facilitate selective elevation of RVP, measured by cannulation of the adrenal vein. A customized recording electrode was implanted around the left renal nerve bundle for direct recording of RSNA.

RESULTS

Clear, characteristic bursts of RSNA were recorded at baseline and during selective elevation of RVP to 10, 20 and 30 mmHg. Quality of RSNA signals was unaffected by mechanical manipulation required to elevate RVP. Pilot results indicate that RSNA increased 32±10% above baseline in response to elevation of RVP (20.1±2.8 vs 26.0±2.2 spikes/sec). True, baroreflex-entrained RSNA was validated by effective silencing of RSNA in response to phenylephrine-induced increase in MAP and the converse activation of RSNA in response to reduction in MAP.

CONCLUSIONS

A novel, sophisticated surgical model allowing direct recording of RSNA in response to experimental manipulation of RVP has been established and validated. Emerging results indicate elevated RVP may directly stimulate increased RSNA.

Supervisor: Dr. Branko Braam

Back to Previous Page

Adherence to an Anti-Inflammatory Diet for 6 Months Can Decrease Fecal Calprotectin in Ulcerative Colitis Patients: Preliminary Findings of a Randomized Controlled Trial

Ammar H Keshteli, Rosica Valcheva, Cheryl Nickurak, Brendan P Halloran, Sander van Zanten, Karen Kroeker, Richard N Fedorak, Karen Madsen, Levinus A Dieleman
Supervisor: Dr. Karen Madsen and Dr. Leo Dieleman

INTRODUCTION

There are sparse data on the role of diet in reduction of ulcerative colitis (UC) relapse. The aim of this study was to assess the effectiveness of a dietary intervention for maintenance of remission in UC patients.

METHODS

In this 6-month RCT, adult UC patients in clinical remission who had a clinical relapse during the previous 18-months were randomized to either an "Alberta-based Anti-inflammatory Diet" or to a diet based on Canada's Food Guide. Patients in the intervention group received dietary counselling in 4 face-to-face interviews(baseline, month1,3,6) and three telephone interviews (month 2,4,5). The anti-inflammatory diet was designed to increase patients' intakes of probiotics, prebiotics, soluble fibers, omega-3 PUFA and decrease red meat intake. The primary outcome was clinical flare and secondary outcomes were changes in serum C-reactive protein (CRP), quality of life (assessed by short inflammatory bowel disease questionnaire(SIBDQ)), and fecal calprotectin (FC). All were assessed at baseline and at month 6/or flare.

RESULTS

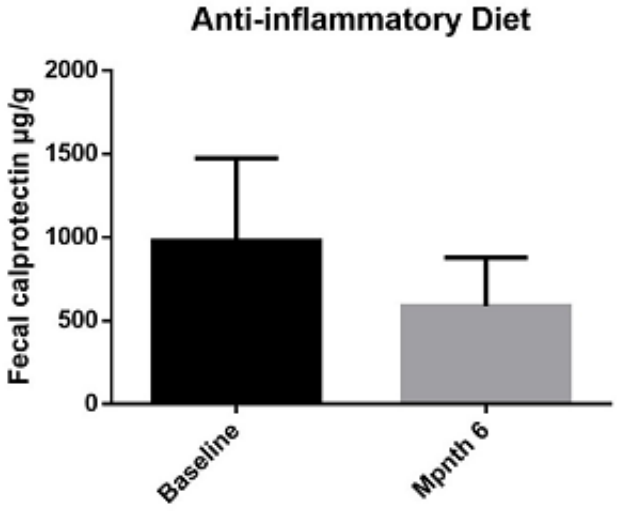
To date, 28 adult UC patients were randomized to the two diet groups. Mean age was 37.7±15.0 years and 16 patients(57.1%) were females. After the 6-month intervention, patients who were randomized to the control group had a 3-fold increase in mean FC levels from baseline, while patients on the anti-inflammatory diet had a 50% decrease in their FC levels(Fig. 1). Four patients(28.6%) in the control and 5 patients(35.7%) in the intervention group relapsed(P=1.0). There was no statistically significant difference between the two diet groups in terms of changes in mean serum CRP and SIBDQ scores during the study.

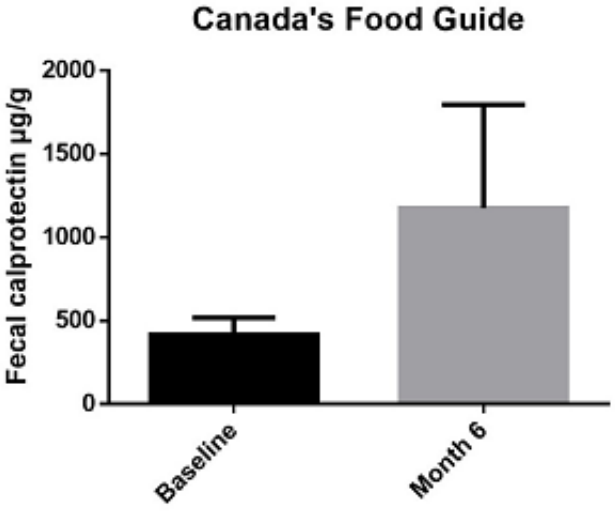
CONCLUSIONS

Dietary counselling and increased intake of anti-inflammatory foods appear to be effective in reducing FC levels in UC patients. These encouraging preliminary findings will need to be confirmed in a larger sample size. Further investigations into the protective mechanisms are pending.

Supervisor: Dr. Karen Madsen and Dr. Leo Dieleman

Back to Previous Page





Back to Previous Page

A Clinical Heuristic to Determine the Likelihood of Typical Adult-type Pulmonary Tuberculosis

Courtney Heffernan, Mary-Lou Egedahl, Alexander Doroshenko, Ambikaipakan Senthilselvan, James Barrie, Richard Long
Supervisor: Dr. Richard Long

INTRODUCTION

The timely diagnosis of typical adult-type smear-positive pulmonary tuberculosis (PTB) is critical to interrupting transmission, improving treatment outcomes, and reaching TB elimination targets. Developing a tool to predict PTB among suspect cases in clinical settings could help achieve these aims.

METHODS

For purposes of developing an evidence-based prediction model for the timely diagnosis of PTB, a comprehensive dataset of cumulative cases suspected of having PTB and being seen in the Edmonton TB Clinic (ETBC) was compiled and analyzed on the basis of 7 clinical rubrics: 1) respiratory and constitutional symptoms, 2) absence of dyspnea, 3) subacute or chronic symptomatology, 4) failure to respond to broad spectrum antibiotics, 5) epidemiologic risk of infection, 6) risk factors for reactivation of latent TB infection and 7) anemia with a normal or low leukocyte count. Suspect cases were scored on the basis of each rubric using a scale of 1 to 4 resulting in a maximum cumulative score of 28. Chest radiographs for cases and non-cases were reported as “typical” or “atypical” for adult-type PTB by an expert reader.

RESULTS

To date, 76 smear-positive, 57 smear-negative and 61 non-cases have been assessed. Average scores were 20±2, ±, 17.4±3.3 and 13.6±1.9, in smear-positive, smear-negative and non-cases, respectively ($p<0.001$). Typical chest radiographic features were present in 76%, 56% and 2% of smear-positive, smear-negative and non-cases, respectively ($p<0.001$). See descriptive table.

CONCLUSIONS

We anticipate being able to derive a prediction equation that determines the likelihood of smear-positive PTB with a typical chest radiograph among patients assessed on the suspicion of having TB in the ETBC, and validating its performance with a 6-month prospectively collected dataset. Supported by a grant from the University Hospital Foundation.

Supervisor: Dr. Richard Long

Back to Previous Page

Table: Cumulative scores on consecutive PTB cases and non-cases to date*

Cumulative score	Cases				Non-Cases	
	S^+C^+ PTB		S^-C^+ PTB		S^-C^- PTB	
	Typical (n = 58)	Atypical (n = 18)	Typical (n = 32)	Atypical (n=25)	Typical (n =1)	Atypical (n = 60)
≥ 21	25	6	5	8		1
18-20	26	10	4	10		1
15-17	6	2	12	4	1	9
≤14	1		11	3		49

Abbreviations: S^+ smear-positive; S^- smear-negative; C^+ culture-positive

* Typical and atypical refers to the chest radiograph interpretation

Back to Previous Page

A Case of Scrotal Tophaceous Gout and Review of the Literature

Sarah A. Henni, Mohammed S. Osman, Anthony S. Russell
Supervisor: Dr. A. Russell

INTRODUCTION

Tophaceous gout is a complication resulting from hyperuricemia, uric acid crystals and chronic inflammation. It most commonly affects the digits, pre-patellar and olecranon bursae and helix of the ear; although it has been reported to deposit in other places such as over the Achilles tendon.

METHODS

Here, we present a 43 year old male with a long standing history of seronegative inflammatory arthritis and chronic kidney disease with chronic tophaceous gout affecting his foot digits, helices of his ears and scrotum and penis.

RESULTS

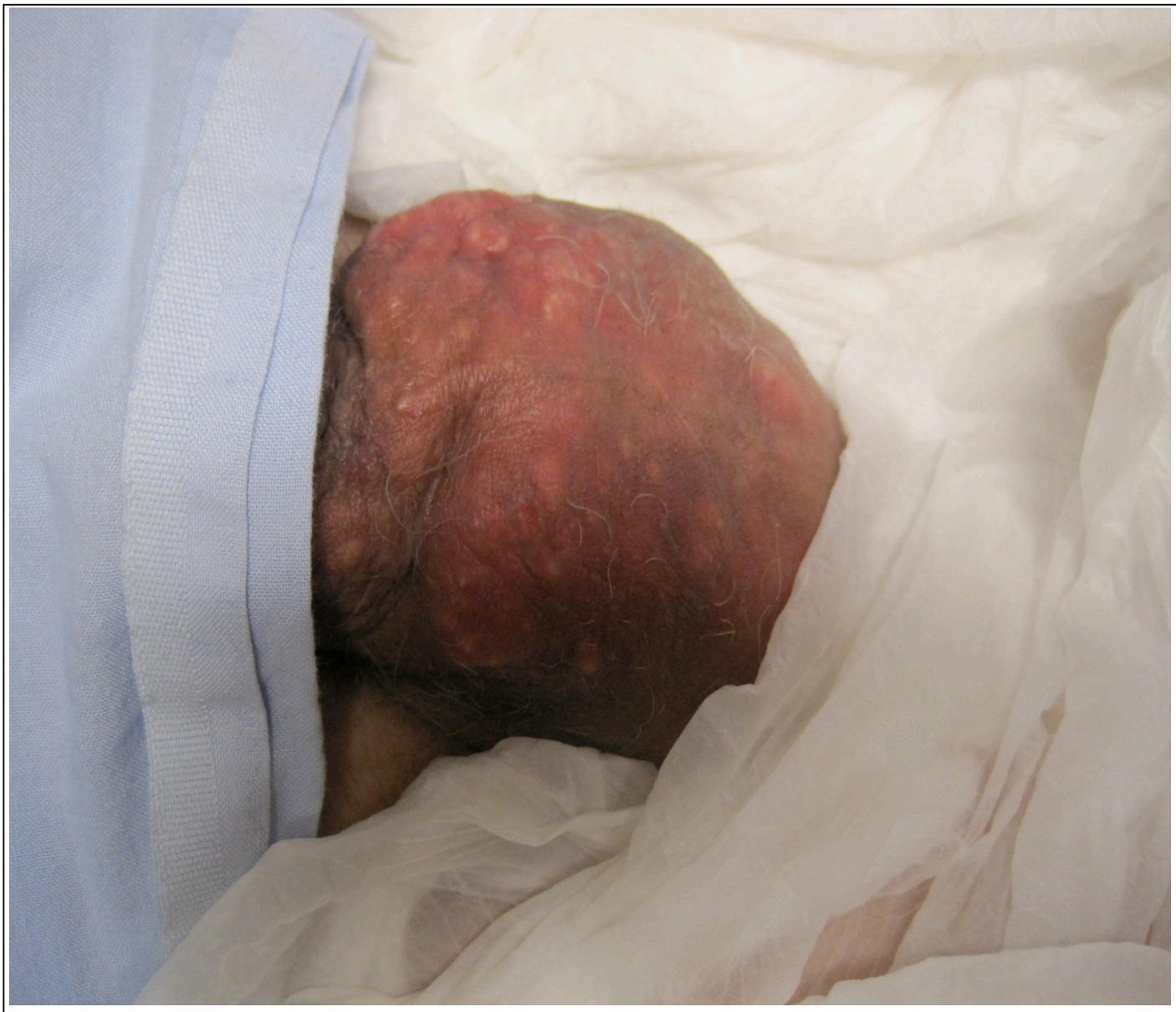
Our patient is a 43 year old male that presented with multiple firm painless nodules in his scrotum which progressively doubled and extended into the shaft of his penis. Eventually, the nodules were associated with intermittent acute erythematous periods ultimately erupting into exudative discharge associated with white chalky discharge. A scrotal ultrasound suggested calcified subcutaneous nodules. Despite numerous topical and laser treatments, the lesions continued to progress. As a result, his scrotum was surgically resected with pathology in keeping with uric acid crystals. Retrospectively, his urate levels were markedly elevated near 785 microM and his baseline estimated glomerular filtration rate was approximately 35 (insert units). Because of his underlying renal dysfunction, he was started on Febuxostat 80 mg and Colchicine 0.6 mg daily with successful reduction of urate level to 452 microM.

CONCLUSIONS

Tophaceous gout affecting the scrotum is very uncommon, as only two other cases have been reported in the literature. Our patient is the only reported case with inflammatory arthritis and scrotal tophaceous gout. Our case highlights the importance of obtaining a tissue diagnosis in directing appropriate definitive therapy.

Supervisor: Dr. A. Russell

Back to Previous Page



Back to Previous Page

The Meaning of Symptoms: Illness Narratives as a Means for Describing Self-Perceived Impacts of H. pylori Infection among Residents of an Arctic Community.

Megan J. Highet1, Amy Colquhoun2, Gladys Edwards3, Billy Archie3, Karen Goodman1,2, and the CANHelp Working Group.
Supervisor: Dr. Karen Goodman

INTRODUCTION

H. pylori represents an important health disparity for people living in the Canadian circumpolar north given that residents of this area have an elevated prevalence of this infection and associated digestive diseases relative to inhabitants of other regions of the country. Yet, quantitative measures of ill-health constitute only part of the overall picture of the health burden posed by H. pylori infection in the arctic. Thus, while a few studies have investigated the epidemiology of H. pylori infection in the Canadian north, less attention has been directed at understanding the social implications of this bacterium with respect to sickness, illness, and disease, which represent the separate but interrelated perspectives of society, the patient, and the health care provider, respectively.

METHODS

The aim of this report is to present the results of a pilot project being conducted in Aklavik, NT using an ethnographic approach to capture and document social and cultural dimensions of ill-health stemming from H. pylori infection. Interviews with community members will produce personal illness narratives, which constitute individual accounts of each person’s story with regard to their experiences surrounding H. pylori as a sickness, an illness, and a disease.

RESULTS

Just as there is no culture-free way to think about disease, neither can a particular cause of ill-health be meaningfully understood apart from the social and cultural implications that it carries for those for whom it causes disease. Considered alongside biomedical frameworks, illness narratives constitute a powerful tool for solidifying multiple perspectives and ways for knowing cross-culturally.

CONCLUSIONS

In the case of H. pylori, this approach serves as a means by which culturally relevant insight regarding social and cultural dimensions of H. pylori infection can be meaningfully incorporated into both health research and medical practice in northern communities.

Supervisor: Dr. Karen Goodman

Back to Previous Page

Routine Serum Protein Electrophoresis Does Not Predict the Development of Post-Transplant Lymphoproliferative Disorder in Heart Transplant Patients: A Quality Improvement Project.

Mark Hnatiuk, Carlos Cervera, Curtis Mabilangan, Anthea Peters
Supervisor: Dr. Anthea Peters

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication following cardiac transplantation. Previous studies in liver transplant recipients indicate the detection of protein gammopathy by serum protein electrophoresis (SPE) may be an effective screening tool for PTLD. The University of Alberta adult heart transplant program monitors most patients with routine annual SPE.

METHODS

All heart transplant recipients between January 1, 2005 and December 31, 2009 (n=189, 65 pediatric, 124 adults) were identified. Pre- and post-transplant SPEs between January 1, 2003 and December 31, 2014 were reviewed. PTLD cases were identified by cross-referencing a database of all PTLD cases diagnosed in Alberta from 1986-2014.

RESULTS

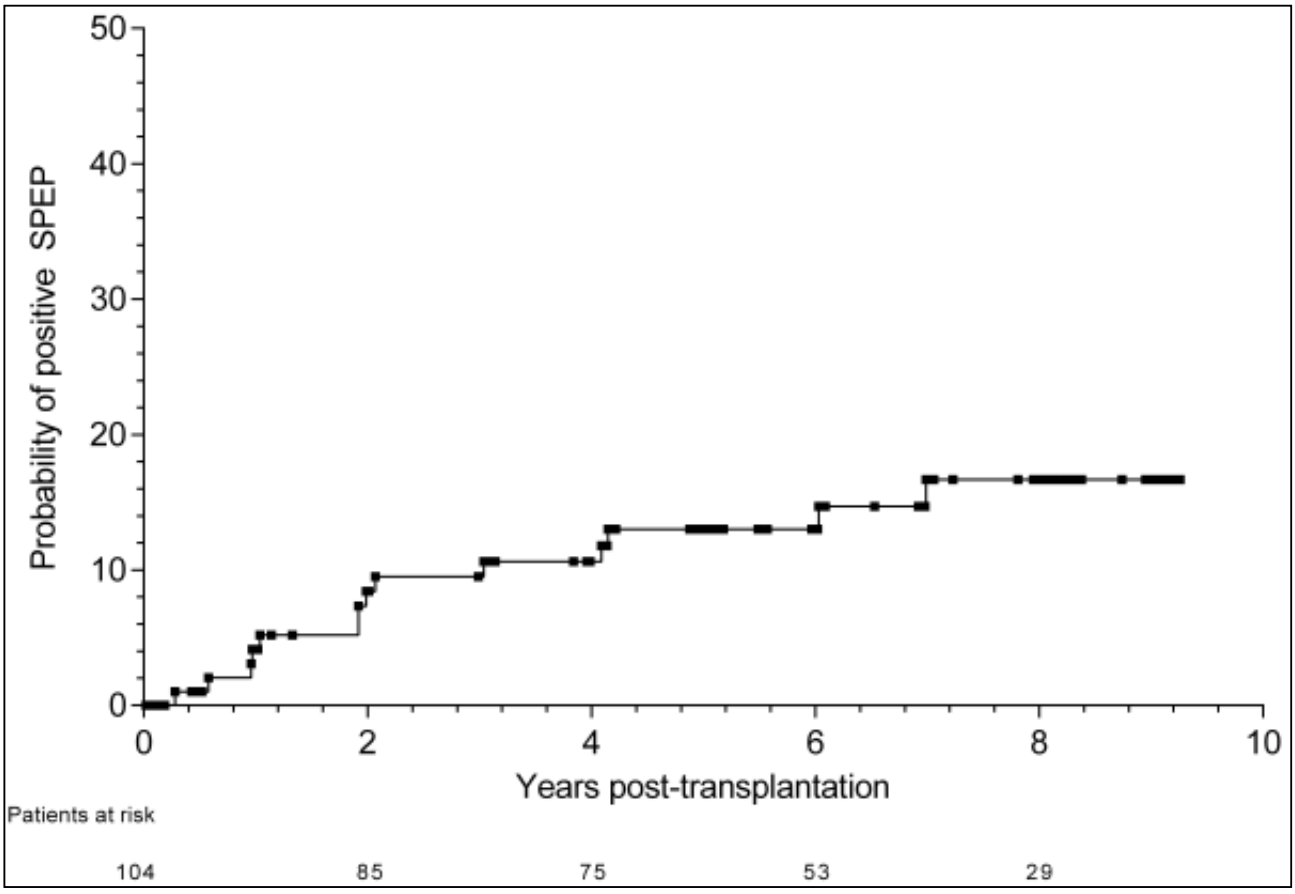
Among 189 cardiac transplant patients, 126 (67%) were male and median age was 43 years (range 0-75). Pre-transplant SPEs were performed in 99 patients (52%); 4 (4%) had abnormal SPEs (all polyclonal gammopathies), but none developed PTLD (p=1.000). One hundred four patients (55%) had at least one post-transplant SPE performed (median 6 tests (interquartile range 4-8)) over 2,200 median follow-up days (interquartile range 1,274-2931 days). Post-transplant gammopathies (monoclonal, oligoclonal, polyclonal, or equivocal) developed in 14 patients (Figure 1), but none developed PTLD. Monoclonal gammopathy greater than 1g/L was observed in 3 patients (21%). All cases of gammopathy eventually resolved on follow-up testing. Seven patients (4%) developed PTLD during the follow-up period, including histologic subtypes of early lesions (n=3, 43%), polymorphic PTLD (n=1, 14%), and monomorphic PTLD (n=3, 43%). Among the 7 cases of PTLD, only one patient had been screened with a post-transplant SPE, and no gammopathy was detected in this case.

CONCLUSIONS

Our data analysis shows that a monoclonal or polyclonal gammopathy on SPE pre- or post-cardiac transplant was not predictive of PTLD. SPE is a relatively expensive lab test. The use of SPE monitoring should therefore be abandoned in this population.

Supervisor: Dr. Anthea Peters

Back to Previous Page



Back to Previous Page

Administrative data are not sensitive for the detection of peripheral artery disease in the community

Yongzhe Hong, Meghan Sebastianski, Mark Makowsky, Ross Tsuyuki, M. Sean McMurtry
Supervisor: Dr. M. Sean McMurtry

INTRODUCTION
We sought to evaluate whether case ascertainment using administrative health data would be a feasible way to identify peripheral arterial disease (PAD) patients from community.

METHODS
Subjects' ankle brachial index (ABI) scores from two previous prospective observational studies were linked with data from three administrative databases from April 2002 to March 2012, including the Alberta Inpatient Hospital Database (ICD-10-CA/CCI), Ambulatory Care Database (ICD-10-CA/CCI), and the Practitioner Payments Database (ICD-9-CM). We calculated diagnostic statistics for putative case definitions of PAD consisting of individual code or sets of codes, using ABI score ≤ 0.90 as the gold standard. Multivariate logistic regression was performed to investigate additional predictive factors for PAD. Different combinations of diagnostic codes and predictive factors were explored to find out the best algorithms for identifying a PAD study cohort.

RESULTS
A total of 1459 patients were included in our analysis. The average age was 63.5 years, 66% were male, and the prevalence of PAD was 8.1%. The highest sensitivity 34.7% was obtained using the algorithm of at least one ICD diagnostic or procedure code, with specificity 91.9%, Positive Predictive Value (PPV) 27.5% and Negative Predictive Value (NPV) 94.1%. The algorithm achieving the highest PPV of 65% was age ≥70 years and at least one code within 443.9 (ICD-9-CM), I73.9, I79.2 (ICD-10-CA/CCI) or all procedure codes, validated with ABI< 1.0 (sensitivity 5.56%, specificity 99.4% and NPV 84.6%).

CONCLUSIONS
Ascertaining PAD using administrative data scores was insensitive compared with the ABI, limiting the use of administrative data in the community setting.

Supervisor: Dr. M. Sean McMurtry

Back to Previous Page

Table. ICD Codes for Validation with ABI Scores

ICD-9-CM Code	Disease	Numbers of subjects identified by each code, n, (%)
440	Any atherosclerosis	92 (6.3%)
440.2	Atherosclerosis of native arteries of the extremities	0
440.21	Intermittent claudication	0
440.23	Atherosclerosis, extremities with ulceration	0
443	Other peripheral vascular disease	0
443.9	Peripheral vascular disease, unspecified	14 (1.0%)
ICD-9-CM Code	**Procedure**	
38.08	Incision of vessel, embolectomy, thrombectomy, lower limb arteries	0
38.18	Endarterectomy, lower limb vessels	0
39.25	Aorta-iliac-femoral bypass	0
39.29	Other peripheral shunt or bypass	0
39.50	Angioplasty of non-coronary vessel	0
39.90	Insertion of non-drug-eluting peripheral vessel stent	0
ICD-10-CA Code	**Disease**	
I70	Atherosclerosis	0
I70.2	Atherosclerosis of arteries of extremities	4 (0.3%)
I70.8	Atherosclerosis of other arteries	0
I70.9	Generalized and unspecified atherosclerosis	0
I73	Other peripheral vascular diseases	0
I73.9	Peripheral vascular disease, unspecified	33 (2.3%)
I79.2	Peripheral angiopathy in diseases classified elsewhere (diabetes E10)	23 (1.6%)
E10.50	Type I diabetes mellitus with peripheral angiopathy	0
E10.51	Type I diabetes mellitus with peripheral angiopathy with gangrene	0
E10.59	Type I diabetes mellitus with circulatory complication, unspecified	0
ICD-10-CCI Code	**Procedure**	
1.KG.50.^^	Dilation, arteries of leg NEC (angioplasty, lower limb arteries)	10 (0.7)
1.KG.57.^^	Extraction, arteries of leg NEC (endarterectomy, lower limb arteries)	8 (0.5%)
1.KG.76.^^	Bypass, arteries of leg NEC	11 (0.8%)

Six of the patients were identified with 2 procedure codes.
ABI, ankle brachial index; ICD-9-CM, international classification of diseases, 9th version, clinical modification; ICD-10-CA, international classification of diseases, tenth revision, canada; CCI, canadian classification of health interventions; NEC, not elsewhere classified.

Acute Elevation of Renal Venous Pressure Increases Renal Vascular Resistance via Renal Nerves in Rats

Xiaohua Huang1,Shereen M. Hamza1,2, William A. Cupples3 and Branko Braam1,2
Supervisor: Dr.Branko Braam

INTRODUCTION

Systemic congestion leads to increased renal venous pressure (RVP), which could compromise renal hemodynamic and excretory function, in turn leading to fluid retention and deterioration of the heart failure. However, the underlying pathophysiological mechanisms are poorly understood. In the present study we tested the hypothesis that increases in RVP lead to increased renal vascular resistance (RVR) mediated by the renal nerves.

METHODS

20 male Lewis rats (300-400g) receiving a normal sodium diet were randomly assigned into 4 groups: intact time control (n=5) or increased RVP (n=5); renal denervation time control (n=5) or combined with increased RVP (n=5). Mean arterial pressure (MAP) and RVP were assessed using femoral artery and adrenal/spermatic vein catheters. GFR was measured by FITC inulin clearance. Left renal arterial blood flow (RBF) was directly measured by transit-time flow probe. To increase RVP, the left renal vein was partial occluded for 120 min. For renal denervation (RD), the renal nerves were stripped and painted with phenol to destroy remaining fibers bilaterally.

RESULTS

Elevation of RVP from 0.9±1.0 to 11.5±1.8 mmHg (n=10) did not alter MAP compared to time control in intact (93.8±4.0 mmHg vs 94.2±3.1 mmHg) or RD (81.0±3.9 mmHg vs 78.8±3.9 mmHg) rats. RBF significantly decreased in the intact elevated RVP rats compared with time controls ($p<0.05$). RVR (calculated using the MAP-RVP difference) increased in intact rats compared to controls (14.7±0.5 vs 10.6±0.2 mmHg/(ml/min), $p<0.05$). RD did not prevent a fall in RBF, but completely abolished the RVR increase. Acute modest increase in RVP did not appear to impact GFR.

CONCLUSIONS

Acute elevated RVP induces an immediate reduction in RBF followed by a steady increase in RVR mediated by renal nerves. This could imply that in congested states like heart failure, renal function is compromised by activation of the renal sympathetic nerves in response to elevated renal venous pressure.

Supervisor: Dr.Branko Braam

Back to Previous Page

Voxel-Wise Texture Analysis of Diffusion MRI Reveals Changes in Amyotrophic Lateral Sclerosis

Abdullah Ishaque, Herb Yang, Dennell Mah, Sanjay Kalra
Supervisor: Dr. Sanjay Kalra

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease of the human motor system. There are no objective biomarkers of the disease and clinical MRI only serves to exclude symptom-mimicking disorders. To this end, we utilized a 3D voxel-wise texture analysis (TA) method to assess whole brain fractional anisotropy (FA) maps of ALS patients. We hypothesized that TA on FA maps would show regional changes in ALS patients when compared to healthy controls.

METHODS

We recruited 19 ALS patients and 25 healthy controls and performed DTI scans with a 4.7 T whole-body scanner. Images were preprocessed using FSL. DTI-TK was used for registration and spatial normalization of DTI volumes. Voxel-wise statistical analysis of the normalized FA images was carried out between patients and controls using tract based spatial statistics (TBSS). Whole brain FA images were generated from the preprocessed DTI data for all subjects in their native space for texture feature extraction. Twenty-two corresponding texture feature maps were generated from the FA images using the 3D TA method. Each subject's texture maps were transformed to the DTI template. Texture feature maps were compared between patients and controls using two-sample t-tests in SPM8 while controlling for age.

RESULTS

In patients, we observed a significant decrease in FA ($p < 0.05$, FWE corrected) bilaterally in the precentral gyrus and corpus callosum with TBSS analysis. Several texture feature maps showed significant difference when ALS patients were compared to healthy controls in the precentral gyrus (Fig 1).

CONCLUSIONS

We showed that 3D voxel-wise TA of FA maps can detect differences between ALS patients and healthy controls. Furthermore, these results are in line with white matter changes observed in ALS patients in the literature. We propose that 3D voxel-wise TA can potentially be used as a tool to assess white matter changes using DTI in ALS.

Supervisor: Dr. Sanjay Kalra

Back to Previous Page

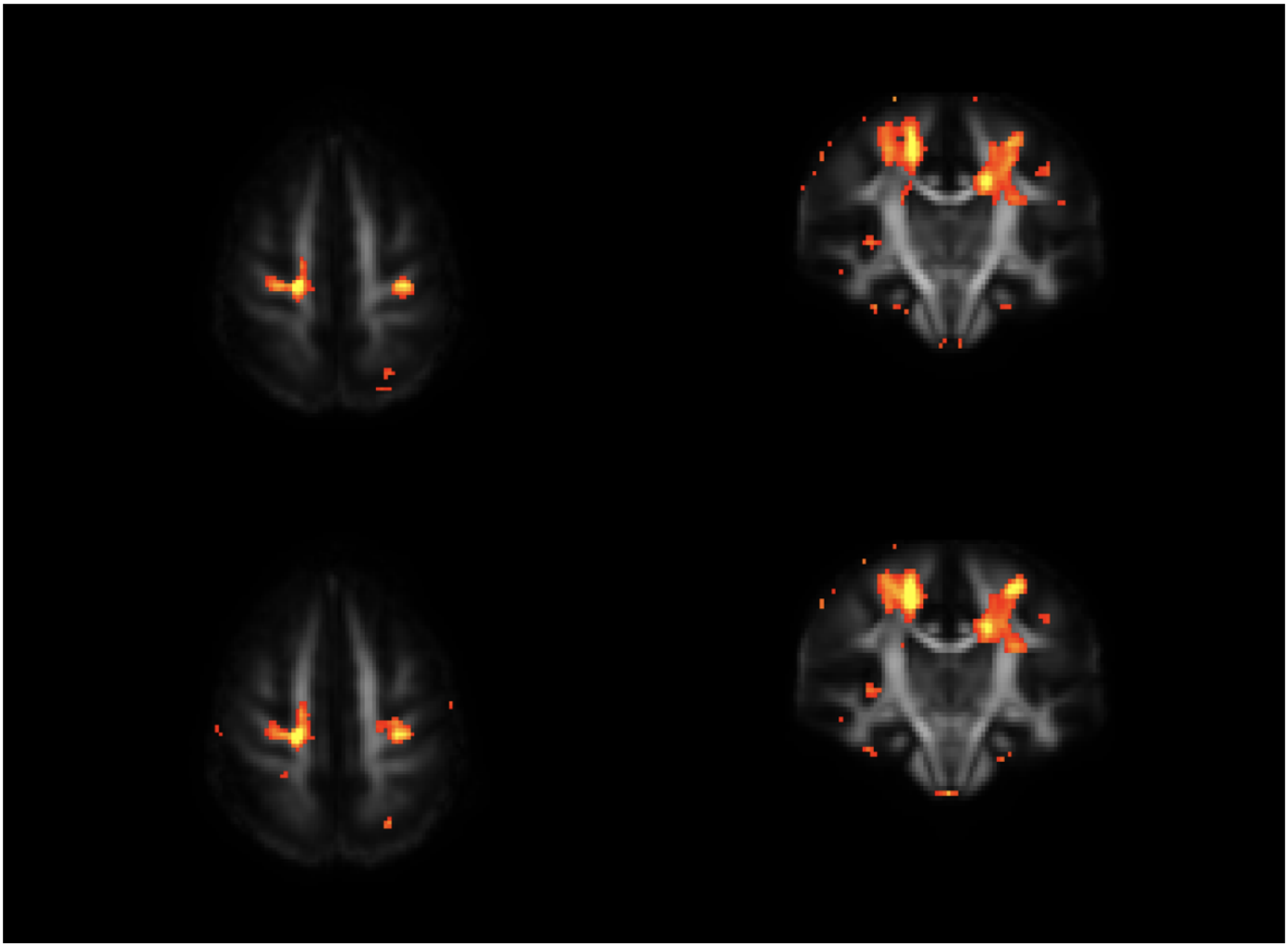


Fig 1: Regional changes in texture of FA images in ALS patients compared to healthy controls, as seen in a representative statistical maps from texture features f_1 (a, b) and f_{22} (c, d). Similar results were found in significant texture features. Areas of red show significant changes ($p < 0.01$, uncorrected) along bilateral precentral gyrus.

Back to Previous Page

MICROARRAY ANALYSIS OF CROHN'S DISEASE AND CORRELATION WITH TRADITIONAL CLINICAL AND HISTOLOGIC FEATURES

Jovanovic V, Chang J, Theisen A, Fedorak R, Halloran P and Halloran B.
Supervisor: Dr. Brendan Halloran

INTRODUCTION

As a T cell-mediated disease of the gastrointestinal epithelium, Crohn’s disease (CD) is likely to share pathogenic elements with other T cell-mediated inflammatory diseases. Recently we showed that ulcerative colitis manifested large-scale molecular disturbances that correlated with endoscopic and histologic features (IBD 20: 2353, 2014). We hypothesized that ileal CD would manifest a similar disturbance.

METHODS

We studied 27 patients in 31 biopsies with ileal CD, characterizing the clinical, endoscopic and histological features and defined the mRNA phenotype using microarray analysis of ileal biopsies. We measured the expression of pathogenesis-based transcript sets (PBTs) previously published for ulcerative colitis representing effector T cells, macrophages, IFNG effects, and parenchymal injury-repair response and dedifferentiation (table 1). The molecular features were then correlated with conventional assessments including clinical features (modified Harvey Bradshaw index(HBI), simple endoscopic score for CD(SES-CD), c-reactive protein, albumin) and histologic features (lamina propria neutrophilic and lymphoplasmacytic infiltrate).

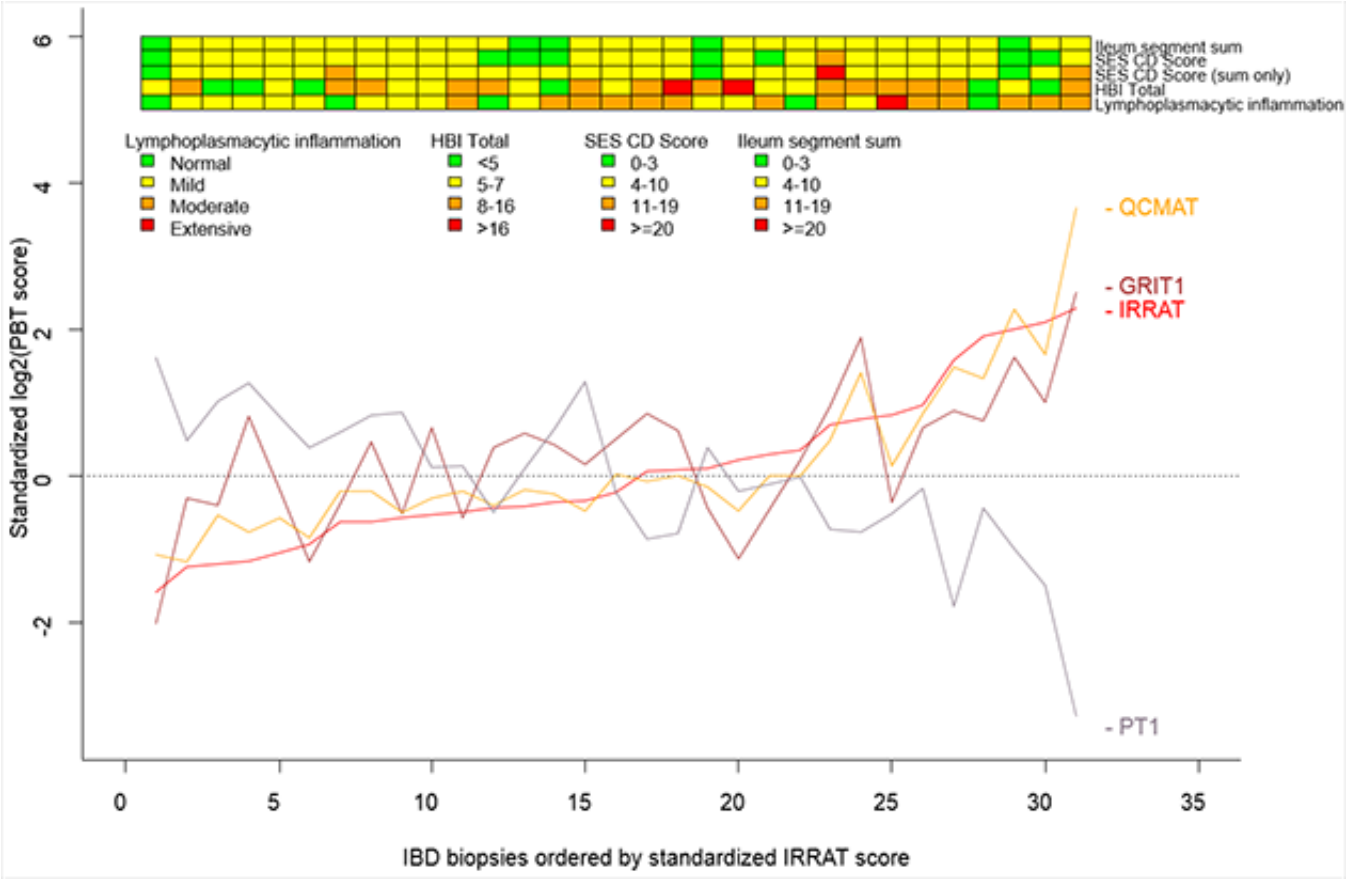
RESULTS

CD ileal biopsies arranged by injury-repair score (IRRAT) manifested coordinate transcript changes with IFNG-induced transcripts (GRIT), macrophage transcripts (QCMAT), and injury-repair transcripts increasing while parenchymal transcripts (PT) decreased (figure 1). Lymphoplasmacytic infiltrate was significantly correlated with IRRAT (P=0.005) and negatively correlated with parenchymal transcript expression (P=0.01). Neutrophilic lamina propria infiltrate (p=0.03) and number of ulcers (p=0.03) also correlated with IRRAT. No significant correlation was seen between the molecular features and the HBI(P=0.5), SES-CD(P=0.8) or CRP(P=0.2).

CONCLUSIONS

The molecular phenotype of CD manifests a large-scale coordinate disturbance similar to that in ulcerative colitis and other T cell-mediated diseases, reflecting changes in inflammatory cells and parenchymal elements and correlating with histologic assessment, especially the lymphoplasmacytic and neutrophilic lamina propria infiltrate, but not with the clinical and endoscopic features. Novel molecular systems for quantitating and staging the disease elements in the tissues in CD may add a significant new dimension to patient management beyond our current standards.

Back to Previous Page



Back to Previous Page

CLINICAL RELEVANCE of The FIRST AVAILABLE 12 LEAD ECG IN PATIENTS WITH SYMPTOMS SUSPICIOUS FOR ACUTE CV DISEASE: Providing Rapid Out of Hospital Acute Cardiovascular Treatment-3 (PROACT-3) ECG SUBSTUDY

R Kashur, Y Zheng, S Sharma, D Weiss, W Tymchak, M Chan, J Ezekowitz, R Welsh
Supervisor: Dr. Robert Welsh

INTRODUCTION

From ECG Core Laboratory analysis in the PROACT-3 study in pre-hospital patients with symptoms suspicious for acute cardiovascular disease; we demonstrated dynamic ECG changes in the majority of patients regardless of their final clinical diagnoses. To address the relevance of these findings we applied a practical approach using clinically relevant ST segment change to assess correlation to: adjudicated diagnoses, peak biomarkers, patient disposition and 30 day death/readmission.

METHODS

PROACT-3 enrolled pre-hospital patients with acute chest discomfort or dyspnea. We analysed subjects with first available ECGs in a core ECG laboratory. Subjects were categorised according to adjudicated diagnoses into: Cardiac including (ACS, AHF and angina), other cardiovascular diagnoses (CV), Chest pain not yet diagnosed (CPNYD) and Non-Cardiac. Magnitude of ST deviation was categorised into normal or abnormal with ST deviation in 2 contiguous leads of: 0.5-1mm, 1.5mm-2mm and ≥ 2.5mm. 422 subjects with analysed ECGs had the following adjudicated diagnoses: Cardiac, Other-CV, CPNYD and Non-Cardiac.

RESULTS

180 subjects had abnormal ECGs which had higher rates of Cardiac and other CV diagnoses than those with normal ECGs ($P=0.004$). In contrast CPNYD and Non-cardiac diagnoses observed less ($P=0.004$). Subjects with abnormal ECGs had higher peak BNP levels ($P<0.001$) and rates of peak BNPs ≥400 ($P<0.001$). Additionally, they had lower rates of discharge ($P=0.002$) and higher rates of receiving (PCI) ($P=0.004$). Moreover, the proportion of subjects with Cardiac and other CV diagnoses increased as the magnitude of ST deviation increased while CPNYD and Non-cardiac diagnoses decreased. Similarly the rates of discharge from ED decreased ($P=0.037$) with increased magnitude of ST deviation. Peak troponin levels positively correlated to the extent of ST deviation ($P=0.001$).

CONCLUSIONS

In Pre-hospital patients with suspected cardiovascular symptoms, the magnitude of ST deviation is directly related to the proportion of number of cardiac diagnoses, peak cardiac biomarkers and need for hospital admissions.

Supervisor: Dr. Robert Welsh

Back to Previous Page

	Normal ECG	Abnormal ECG	P	Abnormal			
				0.5-1 mm	1.5-2mm	>=2.5mm	P
n	242	180		70	75	35	
Adjudicated diagnosis							
Cardiac	49 (20.2)	55 (30.6)	0.004	20 (28.6)	18 (24.0)	17 (48.6)	0.004
Other Cardiac	13 (5.4)	19 (10.6)		4 (5.7)	10 (13.3)	5 (14.3)	
CPNYD	124 (51.2)	65 (36.1)		34 (48.6)	22 (29.3)	9 (25.7)	
Non Cardiac	56 (23.1)	41 (22.8)		12 (17.1)	25 (33.3)	4 (11.4)	
Biomarkers							
Peak BNP (pre/in hospital)	50.0 (12.0, 119.0)	113.5 (26.0, 392.0)	<0.001	45.0 (12.0, 218.0)	199.5 (79.5, 530.5)	133.0 (78.0, 567.0)	0.009
Peak BNP >=400	10 (7.8)	25 (24.5)	<0.001	8 (17.0)	12 (30.0)	5 (33.3)	0.258
Peak trop (pre/in hospital)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)	0.046	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.5 (0.1, 4.4)	0.001
Peak trop >=0.03	121 (71.2)	93 (71.0)	0.972	33 (62.3)	39 (73.6)	21 (84.0)	0.123
Outcomes							
Discharged from ED	185 (76.4)	113 (62.8)	0.002	50 (71.4)	47 (62.7)	16 (45.7)	0.037
30-d Death,	3 (1.2)	4 (2.2)	0.435	1 (1.4)	2 (2.7)	1 (2.9)	0.845
30-d Rehosp/ED	57 (23.6)	37 (20.6)	0.464	9 (12.9)	17 (22.7)	11 (31.4)	0.071
PCI	4 (1.7)	13 (7.2)	0.004	4 (5.7)	4 (5.3)	5 (14.3)	0.198

Back to Previous Page

An individualized and multi-faceted transition intervention is needed for pediatric patients with inflammatory bowel disease

Natalie R. Klostermann (1,5), Laura McAlpine (1), Eytan Wine (3,4,5), Karen J. Goodman (1,2), Karen I. Kroeker (1,5)
Supervisor: Dr. Karen Kroeker

INTRODUCTION

The transition of chronically ill patients from pediatric to adult care can be challenging. Limited resources are available to aid young adults with inflammatory bowel disease (IBD) in this transition. Development of an effective transition intervention requires an understanding of the transition experience, preferred intervention content and format and assessment of young adult IBD patients with respect to skills required for successful transition.

METHODS

This mixed methods study utilized semi-structured qualitative interviews with 20 participants, age 17-20 years, who transitioned during 2013-2015 from the Stollery Children's Hospital to the Zeidler Clinic in Edmonton, Alberta. Three validated assessments were used to evaluate any deficits in self-management/self-advocacy, medication adherence and knowledge of IBD. Interview responses were analyzed thematically. Non-parametric tests were used to compare scores on the assessments to published estimates.

RESULTS

The idea of a transition intervention was well received by study participants. Discussion of preferred content centered on medications, disease and what to expect during transition. The top three preferred methods of intervention were one-on-one with a healthcare practitioner, handouts and websites. Themes generated were "Individualized and Multi-faceted," "Teach about Transition," and "Support the Shift in Responsibility."

As shown in Table 1: participants scored above the published estimate for knowledge. Medication adherence and transition skill scores were comparable to published estimates; however, this means 1/3 of participants had poor adherence, and only 1 out of 20 had mastered 90% of the transition skills.

CONCLUSIONS

Based on this assessment, we are designing an interactive website to address skill deficits and knowledge areas of interest. It will be individualized and multi-faceted, support the shift in responsibility and teach about transition.

Supervisor: Dr. Karen Kroeker

Back to Previous Page

Table 1. IBD knowledge, medication adherence, self-advocacy and self-management scores of participants compared to literature values.

Measure	Participant value	Literature value	*P* value
IBD-KID	15.5(5)*	11.3±0.37†	0.01‡
MMAS-8	32% scored <6 (low adherence)	52% scored <6 (low adherence)	0.23¥
TRAQ	5.3% scored ≥18/20 (≥90% mastery of skills)	5.6% scored ≥18/20 (≥90% mastery of skills)	1.0¥

* Median (IQR) † Mean ± SD ‡ Sign Test ¥ Fisher's Exact Test

Back to Previous Page

Understanding how to salvage peripheral neurons: implications for regenerating nerves

Anand Krishnan, Ambika Chandrasekhar & Douglas W.Zochodne
Supervisor: Dr.Douglas Zochodne

INTRODUCTION

A clear understanding on the intrinsic regulators that mediate injury responses in neurons to distal nerve injuries may offer therapeutic strategies for facilitating peripheral nerve regeneration. We have discovered that the molecules involved with DNA repair, BRCA1, pH2X and 53BP1, are critically altered in neurons after distal nerve injury and impact their ability to recover.

METHODS

Expression of BRCA1, pH2X and 53BP1 were studied using immunohistochemistry. Adult neuron cultures were established from DRG neurons from SD rats. Cisplatin and H2O2 were used to induce toxicity in neurons. Transient knockdown of BRCA1 in primary sensory neurons was done using siRNA.

RESULTS

Both BRCA1 and 53BP1 had intense expression in normal DRG neurons with the former diffusely distributed throughout cytoplasm and nucleus, without clear distinction, and the latter distinctly nuclear. pH2X showed diffuse expression in nuclei that did not identify DNA damage in otherwise intact neurons. After injury, pH2X changed its expression and appeared as granular in some neurons, representing a DNA damage response, accompanied by striking accumulation of BRCA1 in neuronal nuclei. Interestingly, 53BP1 relocated mainly to the cytoplasm in injured neurons. H2O2 mediated oxidative stress or cisplatin treatment also induced granulated nuclear pH2X and BRCA1 in mature adult neurons in vitro indicating involvement of BRCA1 in mediating a DNA damage response. In addition, we noted a positive correlation between nuclear localization of BRCA1 and neurite outgrowth in primary sensory neurons. Finally, transient knockdown of BRCA1 reduced the outgrowth in neurons in vitro indicating a facilitatory role for BRCA1 on neurite outgrowth.

CONCLUSIONS

Our results indicate that distal injury mediated oxidative stress may initiate a DNA damage response in neurons. BRCA1, by virtue of its DNA repair functions, upholds the integrity of regenerating neurons. The involvement of DNA damage and repair in peripheral neurons has implications for the understanding and treatment of neuropathies generally.

Supervisor: Dr.Douglas Zochodne

Back to Previous Page

Normalization of Pulmonary Function after Sleeve Gastrectomy in a Patient with Occupational Asthma

Lorie Kwong, Renuca Modi, Justin Sebastian, Sarah Chapelsky
Supervisor: Dr. Sarah Chapelsky

INTRODUCTION

Increasing adiposity is predicted to play a role in multiple respiratory diseases. There is a well-established association between obesity and asthma. Obesity is a major risk factor for asthma development, and there is a dose-dependent relationship between increasing body-mass index (BMI) and asthma severity. Distinct asthma phenotypes occur in obesity, and these are often poorly responsive to standard treatments. Weight loss improves obese asthma outcomes.

Reactive airways dysfunction syndrome (RADS) is a form of occupational asthma (OA) that results from the inhalation of high concentrations of an irritant. Herein, we describe a patient with class 2 obesity and RADS secondary to aerosolized formaldehyde exposure. Weight loss via surgical intervention resulted in substantial improvement in symptom control and pulmonary function.

METHODS

Initial pulmonary function testing showed reversible airflow obstruction and moderate bronchial hyperreactivity. Despite standard treatment with inhaled corticosteroids, anticholinergics and bronchodilators, asthma control was suboptimal. The patient was assessed in a tertiary weight management clinic for consideration of bariatric surgery. She underwent a sleeve gastrectomy with an uncomplicated postoperative period.

RESULTS

The patient was weight stable prior to surgery with a BMI of 38.4 kg/m^2. She lost 13% of initial body weight in the early postoperative period. With this weight loss, her lung function improved with normalization of FEV1/FVC ratio and FEV1 improved by 260 mL (13%).

CONCLUSIONS

To our knowledge, we are the first to describe improvement in occupational asthma with weight loss. These results support a role for obesity in RADS outcomes, and suggest weight loss as a potential therapeutic intervention.

Supervisor: Dr. Sarah Chapelsky

Back to Previous Page

Real world outcomes of patients with metastatic renal cell carcinoma (mRCC) using first-line sunitinib or pazopanib: the Canadian experience

Aly-Khan A. Lalani1, Haocheng Li2, Daniel Y.C. Heng3, Lori Wood4, Austin Kalirai5, and Naveen Basappa1 for the authours associated with the Canadian Kidney Cancer Information System (CKCis) database
Supervisor: Dr. Naveen Basappa

INTRODUCTION

Standard first-line treatment for mRCC includes VEGF-targeted therapies such as sunitinib and pazopanib. Clinical trial data has shown similar efficacy between these two drugs; however, real world experience in Canadian patients has not been described. We aimed to determine outcomes and compare toxicities of patients with mRCC treated with first-line sunitinib or pazopanib.

METHODS

Data were retrieved from the prospective Canadian Kidney Cancer Information System (CKCis) database from Jan 2011 - Nov 2015. Patients with clear cell mRCC treated with first-line sunitinib or pazopanib were included. Time-to-Treatment Failure (TTF) and Overall Survival (OS) were calculated using Kaplan-Meier methods. Cox regression analysis allowed for adjustment of International Metastatic RCC Database Consortium (IMDC) criteria. Fisher’s exact tests were used to compare dose-modifying toxicities between the two therapies.

RESULTS

Our cohort included 93 patients treated with pazopanib and 577 with sunitinib. Median TTF was greater with sunitinib versus pazopanib (6.0 vs 3.7 months, p=0.046) and maintained significance when adjusted for IMDC criteria (hazard ratio [HR] 0.61, 0.41-0.90 95% CI, p=0.013). Median OS was better in patients treated with sunitinb (31.9 vs 20.6 months, p=0.028) and maintained significance when adjusted for IMDC criteria (HR 0.60, 0.38-0.95 95% CI, p=0.028). Common toxicities requiring dose modification, including fatigue and diarrhea, were similar between both groups (Table 1). However, patients treated with sunitinib had a significantly higher incidence of mucositis, hand-foot syndrome, and GERD; patients treated with pazopanib had a significantly higher incidence of liver toxicity and a trend towards weight loss.

CONCLUSIONS

In Canadian patients with clear cell mRCC, survival and treatment duration appears to favour sunitinib over pazopanib. Plausible explanations include small sample size, potential differences in patient selection for pazopanib, and the contemporary experience with individualized dosing on sunitinib. These data on real world toxicities are informative and may aid physicians and patients in guiding treatment decisions.

Supervisor: Dr. Naveen Basappa

Back to Previous Page

Adverse Event	**Pazopanib (N=93)** – number of patients, (%)	**Sunitinib (N=577)** – number of patients, (%)	**p-value**
Fatigue	23 (25)	168 (29)	0.46
Diarrhea	16 (17)	89 (15)	0.65
Mucositis	**7 (7)**	**94 (16)**	**0.028**
Hand-Foot syndrome	**3 (3)**	**69 (12)**	**0.01**
Hypertension	7 (7)	55 (9)	0.70
Nausea and Vomiting	9 (10)	79 (14)	0.32
Gastroesophageal reflux disease	**1 (1)**	**38 (7)**	**0.031**
Weight loss	7 (7)	20 (4)	0.08
Liver toxicity	**13 (14)**	**15 (3)**	**0.001**
Thrombocytopenia	2 (2)	41 (7)	0.10
Neutropenia	0 (0)	21 (4)	0.09
Anemia	1 (1)	4 (<1)	0.53

Table 1. Selected dose-modifying adverse events during treatment with pazopanib or sunitinib as first-line therapy in metastatic RCC.

Assessment of Islet Engraftment in Clinical Islet Transplantation Using BETA-2 Score

Anna Lam, Richard Oram, Peter Senior
Supervisor: Dr. Peter Senior

INTRODUCTION

The early phase post-islet transplantation (ITx) is critical for islet engraftment. Experimental models show that within the first 2 weeks post-ITx, >60% of transplanted islets undergo cell death and that graft vascularization is complete. Clinically, however, the time course for islet engraftment remains unknown. This is due to the lack of tools for monitoring islet graft function in clinical-ITx; current gold standards are labor and time intensive and therefore impractical clinically. The BETA-2 score is a novel and validated measure of graft function that is calculated from a single blood sample and is therefore easily clinically applicable. Using the BETA-2 score we elucidated the time course of islet engraftment post-transplantation.

METHODS

A retrospective analysis of C-peptide negative islet recipients (2009-2014) who achieved insulin independence after one islet transplantation (1Tx) or required second islet transplantation (2Tx) within 3-6 months was conducted. Weekly post-ITx BETA-2 scores were calculated as [(√fasting C-peptide) x (1-insulin dose)] ÷ [Fasting plasma glucose x HbA1c] x 1000.

RESULTS

16 consecutive islet recipients were included (1Tx, n=9 and 2Tx, n=7). 1Tx patients maintained insulin independence for >1 year. Baseline characteristics were similar (1Tx vs. 2Tx: age 55±11 vs. 49±13 years, male 2/9 vs. 4/7, diabetes duration 32±12 vs. 37±13 years, weight 64.9±7.8 vs. 68.9±15.4 kg; p=ns). BETA-2 increased rapidly by W1, further at W4, remaining stable until W16, but was significantly higher in 1Tx at each time point (table). In 2Tx, BETA-2 increased further 1 week after second infusion, but remained lower than in 1Tx between W18-W24.

CONCLUSIONS

Islet engraftment takes place rapidly over the first week and is complete by 4-6 weeks post-ITx. Our data confirm previous experimental data showing that the early phase post-ITx is critical for islet engraftment. However, it appears that the period of engraftment extends beyond 2 weeks in clinical-ITx compared to experimental models.

Supervisor: Dr. Peter Senior

Back to Previous Page

TREATMENT SUCCESS RATES OF DIFFERENT REGIMENS

Treatment	1st line	2nd line	3rd line	4th line	Total
Sequential	66/80 (82.5%)	2/6 (33.3%)	2/2 (100%)	No data	70/88 (79.5%)
PPI-CA	83/207 (40.1%)	8/33 (24.2%)	1/4 (25.0%)	0/1 (0.0%)	92/245 (37.7%)
PPI-CM	5/25 (25.0%)	2/17 (11.8%)	0/3 (0.0%)	No data	7/45 (15.6%)
Bismuth Quadruple	8/13 (61.5%)	36/67 (53.7%)	20/31 (64.5%)	3/6 (50.0%)	67/117 (57.3%)
PPI-AL	1/2 (50.0%)	2/12 (16.7%)	10/23 (43.5%)	4/5 (80.0%)	17/42 (40.5%)
Miscellaneous	5/9 (55.6%)	6/16 (37.5%)	6/11 (54.5%)	2/2 (100%)	19/38 (50.0%)
Total	168/336 (50.0%)	56/151 (37.9%)	39/74 (52.7%)	9/14 (64.3%)	

Back to Previous Page

Baseline Lung Allograft Dysfunction Negatively Impacts Survival Following Lung Transplantation

Jonathan Liu MD, Jeff Reeve PhD, Kathy Jackson RN, Ali Kapasi MD, Justin Weinkauf MD, Alim Hirji MD, Dale Lien MD, Kieran Halloran MD
Supervisor: Kieran Halloran

INTRODUCTION

Chronic lung allograft dysfunction (CLAD) is the progressive loss of function in the transplanted lung over time, and remains a major factor limiting long term survival in lung transplant recipients. It is defined as deterioration from a stable post transplant “baseline,” but the role of the baseline itself is understudied. Our objective was to identify a subset of patients with baseline dysfunction, the relationship to survival and potential clinical risk factors.

METHODS

We conducted a retrospective cohort study of all double lung transplant recipients in the University of Alberta Lung Transplant program from 2004 and 2009 (n=178). We defined normal baseline as a forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) > 80% on two consecutive measurements > 3 weeks apart, at any point post-transplant. We analyzed the impact on survival as a time dependent covariate in a Cox proportional hazards regression model. We also assessed potential risk factors for baseline dysfunction as the outcome of interest with multivariable regression.

RESULTS

75/178 (42%) patients had baseline dysfunction. The hazard ratio for death in recipients with baseline dysfunction was 2.2 (LL 1.4, UL 3.5, $p < 0.01$). Median time to peak lung function in those with baseline dysfunction was 269 days, compared to 536 days in normal controls ($p < 0.01$). Of candidate risk factors assessed, both interstitial lung disease (ILD) as indication for transplant (OR 2.2, p=0.04) and prolonged post operative mechanical ventilation time (OR 1.002/hour, p=0.01) were associated with baseline dysfunction in multivariable analysis.

CONCLUSIONS

Failure to achieve normal baseline function following double lung transplant negatively impacts survival, and is associated with pretransplant ILD and prolonged post-operative ventilation time. Our results support the integration of baseline function into potential CLAD phenotyping algorithms and its further evaluation as a discrete clinical entity.

Supervisor: Dr. Kieran Halloran

Back to Previous Page

Characteristic	Value	Normal	Baseline dysfunction	p-value
Baseline lung allograft dysfunction (%)	178	75 (42)	103 (58)	-
Follow up in days, median (25^{th},75^{th} quartile)	2283 (1640, 2923)	-	-	-
Recipient age in years, median (SD)	55.5 (39, 60)	60 (52, 63)	57 (39,60)	0.36
Diagnosis (%)				0.06*
Obstructive lung disease	80 (45)	51 (50)	29 (39)	
Interstitial lung disease	52 (29)	22 (21)	30 (40)	
Bronchiectasis	39 (22)	25 (24)	14 (19)	
Vascular disease	7 (4)	5 (5)	2 (3)	
Recipient BMI, median (25^{th}, 75^{th} quartile)	24 (20,28)	23 (20,27)	26 (19,30)	<0.01*
CMV mismatch (%)	33 (19)	20 (19)	13 (17)	0.85
Bridging, ventilation or ECLS (%)	8 (4)	5 (5)	3 (4)	1
Rejection (within 3 months) (%)	40 (22)	26 (25)	14 (19)	0.36
Primary graft dysfunction (Grade 3) (%)	49 (28)	25 (24)	24 (32)	0.31
Hospital stay in days, median (25/75^{th} quartile)	27 (20, 52)	22 (17,34)	39 (22, 81)	<0.01*
Ventilation in hours, median (25^{th},75^{th} quartile)	63 (36, 180)	57 (36, 110)	114 (50,352)	0.01*
Donor age, median (25^{th},75^{th} quartile)	37 (21, 51)	33 (22,49)	47 (21,53)	0.04*
Donor smoking status, current or prior (%)	111 (64)	64 (64)	47 (64)	0.89
Donor O2 challenge in mmHg, mean (SD)	412 (77)	421 (77)	400 (75)	0.08*
Positive crossmatch by flow cytometry (%)	20 (12)	12 (8)	8 (11)	0.82
Total graft ischemic time in minutes, mean (SD)	355 (120)	351 (120)	363 (121)	0.49
Prior thoracic surgery (%)	38 (21)	18 (17)	20 (27)	0.14
Major size mismatch ($\geq$ or $\leq$ 10cm) (%)	19 (11)	12 (12)	7 (9)	0.80

Back to Previous Page

Correlation between endothelial cell heterogeneity and expression of VWF in distinct organs.

Areli Lorenzana-Carrillo, Anahita Mojiri, Nadia Jahroudi
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Endothelial cells (EC) of different organs exhibit heterogeneity in structure, function and gene expression. This also extends to the pattern in which the highly endothelial specific gene, von Willebrand Factor (VWF) is expressed. It was demonstrated that EC specific proximal promoter of the VWF gene exhibits organ-specific activity. We hypothesised that pattern of expression of transcription factors that regulate the VWF promoter activity may contribute to the mechanism that governs organ-specific regulation of VWF promoter activity.

METHODS

Immunofluorescence staining was used in various murine organs to mark the VWF and CD31 expressing EC. We also co-stained for specific transacting factor GATA isoforms (GATA2, 3 and 6) that were shown to interact with and function as activator of the VWF promoter.
Laser Capture Microdissection (LCM) was used to mark and dissect 1 to 10 cells of 3 sets of different cells of lung and heart including; VWF and CD31 expressing EC, EC expressing CD31 alone, and cells that were not EC and did not expressed VWF or CD31. RT-PCR was used to analyse gene expression pattern in the dissected cells.

RESULTS

Our IF and confocal microscopy demonstrated that ECs of distinct organs exhibit distinct patterns of GATA isoforms. Using IF and LCM we were able to positively identify, capture and isolate target cells. RT PCR analyses of isolated target cells demonstrated significant VWF expression in dissected EC, which was comparable to cultured EC.

CONCLUSIONS

These data suggest that we have an organ specific expression pattern of transcription factors that participate in VWF transcription. The use of laser capture microdissection system will allow us to specifically detect the expression pattern of distinct regulatory factors that participate in regulation of the VWF gene in EC of distinct organs.

Supervisor: Dr. Nadia Jahroudi

Back to Previous Page

Tackling the ‘In-between’ in the Implementation of Complex Interventions: the 5As Team Intervention to Improve Weight Management in Primary Care

T Luig, J Asselin, AM Sharma, DL Campbell-Scherer
Supervisor: Dr. Denise Campbell-Scherer

INTRODUCTION

Transforming research knowledge for use in complex practice settings has proven challenging. The lack of solid theoretical understanding to guide design and evaluation of implementation of complex interventions has resulted in the development of a number of theoretically informed frameworks. Yet, they rarely detail the complex interactions that impact implementation processes. Improving obesity management in primary care faces multiple complexities: a multifactorial condition, comorbidities, activation of a diverse patient population, and interdisciplinary teams of clinicians within unstable structural environments. The 5As Team Intervention to improve weight management in a Primary Care Network (PCN) team made an explicit effort to document the implementation process as it played out in context. The present work will report our findings on the 5AsT implementation strategy and use them to further develop a framework for dissemination and implementation, the Interactive Systems Framework, with particular attention to interactions, knowledge pathways, and processes in-between the framework’s components.

METHODS

Secondary qualitative analysis of relevant codes and patterns related to the 5AsT implementation process. Review of 61 models and frameworks for dissemination and implementation.

RESULTS

Increase in interdisciplinary relationships, communication, and confidence emerged as both an intervention outcome and a facilitator of implementation success. Dynamic design of iterative evaluation and flexible implementation strategy proved crucial for sustainable, context-appropriate intervention impact. Collaboration with PCN staff and management throughout the project ensured a positive implementation environment and the transformation of evidence into knowledge-in-practice-in-context. Findings support the focus on collaboration, capacity building, and communication proposed by the Interactive Systems Framework.

CONCLUSIONS

Results illuminate under-researched processes and interactions that impact implementation processes. Sustained engagement that respects tacit knowledge and contextual expertise, as well as dynamic evaluation and intervention design proved effective for multi-directional knowledge exchange and enabled the co-creation of contextually relevant knowledge-in-practice.

Back to Previous Page

A Novel Gerstmann-Sträussler-Scheinker Disease insertion mutation in the Prnp gene causes disease in transgenic mice.

Robert C.C. Mercer, Lyudmyla Dorosh, Charles E. Mays, Nathalie Daude, Serene L. Wohlgemuth, Jing Yang, Hristina Gapeshina, Holger Wille, Michael B. Coulthart, Gerard H. Jansen, Maria Stepanova and David Westaway
Supervisor: Dr. David Westaway

INTRODUCTION

Prion diseases are invariably fatal neurodegenerative diseases with an etiology that is sporadic, acquired through infection or genetic. The central event in these diseases is the structural transition of the primarily α-helical prion protein (PrPC) to a disease-associated conformer with an increased proportion of β-structure (PrPSc). A genetic human prion disease, Gerstmann-Sträussler-Scheinker Disease (GSS) is caused by mutations of the gene encoding PrPC (PRNP). Recently, a novel insertion mutation in PRNP was discovered that resulted in the extension the hydrophobic region (HR) of PrPC by 8 amino acid residues. The HR is the most highly conserved segment of PrPC and is implicated in early structural rearrangements considered “on-pathway” to PrPSc.

METHODS

Molecular Dynamics simulations, biochemistry, transgenesis, histopathology

RESULTS

Molecular dynamics (MD) simulations utilizing this novel allele revealed a relatively unstable molecule with an increased proportion of β-sheet content. Transgenesis was then used to explore the pathogenic potential of this striking allele. We created a mouse Prnp allele with LGGLGGYV inserted between residues 127/128 (Tg.PrPHRdup) as well as a control M128V allele to match the V129 allelic origin of the founder mutation (Tg.PrP128V). Tg.PrPHRdup mice develop a spontaneous neurologic syndrome at ages >300 days, whereas Tg.PrnpM128V mice did not. Histopathological and biochemical profiling of these mice has defined chemically resistant PrP deposits and vacuolation as well as a protease resistant 7 kDa PrP fragment, a hallmark of GSS that is also observed in patients. Onset of clinical symptoms in Tg.PrPHRdup mice could be accelerated through intracranial inoculation with brain homogenate from clinically ill animals, demonstrating transmissibility under certain conditions.

CONCLUSIONS

These mice are the first model of GSS that recapitulate both the biochemical and neurological hallmarks of the disease and, therefore, prove to be useful in future drug studies.

Supervisor: Dr. David Westaway

Back to Previous Page

Von Willebrand factor expression by cancer cells of non-endothelial origin and its functional consequences

Anahita Mojiri , Konstantin Stoletov , Lian Willetts , Roseline Godbout , Paul Jurasz , Consolato M. Sergi , David D. Eisenstat , John D. Lewis , and Nadia Jahroudi
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Von Willebrand factor (VWF) is a highly adhesive procoagulant molecule that mediates platelets adhesion to endothelial and subendothelial surfaces. Normally it is expressed exclusively in endothelial cells and megakaryocytes. However, few studies have reported VWF detection in cancer cells of non-endothelial origin, including osteosarcoma SAOS2. Increased plasma levels of VWF and alterations in coagulation system in cancer patients with metastasis and cancer progression are reported. A role for VWF in cancer metastasis has long been postulated but evidence supporting both pro- and anti-metastatic role for VWF have been presented. We hypothesized that the role of VWF in cancer metastasis may be influenced by its cellular origin and that if cancer cells acquire VWF expression, this may contribute to their enhanced metastatic potential.

METHODS

- For VWF expression RT-PCR, western blot and immunofluorescence analyses were used. For transcription factor binding and epigenetic modifications Chromatin Immunoprecipitation was used. Functional analysis included cell-adhesion and Chick Chorioallantoic Membrane assays. Extravasation ability of cancer cells was examined in mice model.

RESULTS

We demonstrated de novo expression of VWF at the RNA and protein levels in a number of glioma as well as SAOS2 cell line. Endothelial monolayer adhesion, transmigration and extravasation capacities of VWF expressing cancer cells were enhanced compared to non-VWF expressing osteosarcoma KHOS, and significantly reduced as a result of VWF knock down. VWF expressing cancer cells were also detected in few patient tumor samples that were analyzed. Analyses of the mechanism of transcriptional activation of the VWF in cancer cell lines demonstrated a pattern of transacting factors bindings and epigenetic modifications that was generally consistent with that observed in endothelial cells.

CONCLUSIONS

These results demonstrate that cancer cells of non-endothelial origin can acquire de novo expression of VWF, which can enhance metastatic processes, including endothelial and platelet adhesion and extravasation.

Supervisor: Dr. Nadia Jahroudi

Back to Previous Page

Endothelial cells of distinct organs exhibit heterogeneity in response to hypoxia with regard to von Willebrand factor transcriptional regulation

Anahita Mojiri, Maria Areli Lorenzana Carrillo, Radya Yousef Abdualla, Maryam Nakhaei-Nejad, Bernard Thebaud, William C. Aird, Nadia Jahroudi
Supervisor: Dr. Nadia Jahroudi

INTRODUCTION

Von Willebrand factor (VWF) expression is heterogeneous in vivo and responds to hypoxia differentially in distinct vascular beds. Our objectives in the current studies were to determine mechanisms that govern organ-specific transcriptional activity of VWF in response to hypoxia; specifically in human cardiac versus lung endothelial cells (ECs). We also aimed to determine the functional consequences of differential VWF response to hypoxia in distinct vascular beds.

METHODS

ECs of various organs were used to determine their response to hypoxia with regard to VWF expression. Adenoviral vectors containing various VWF regulatory regions fused to LacZ gene were generated to determine regulatory element that mediate hypoxia response of VWF in heart versus lung. Chromatin IP analysis and DNA methylation assessment were performed to determine transcription factors binding pattern, as well as epigenetic modification on the VWF promoter. siRNA against various VWF regulatory transacting factors were used to determine their role in hypoxia induction of VWF. Vascular beds of various organs of mice exposed to hypoxia and control were analyzed for the presence of microthrombi.

RESULTS

Differential hypoxia response of VWF gene in human EC of distinct organs in vivo was reflected in cultured endothelial cells of corresponding organs. EC of heart and lung employed distinct regions of VWF regulatory sequences for hypoxia response. Distinct patterns of transacting factors interaction with the VWF promoter in lung and heart EC in response to hypoxia were demonstrated. VWF upregulation in response to hypoxia was also concomitant with presence of thrombi in heart and lung but not vascular beds of organs that did not upregulate VWF in response to hypoxia.

CONCLUSIONS

Although hypoxia induction of VWF occurs in ECs of both heart and lung, they employ distinct mechanisms. Hypoxia induced VWF upregulation were associated with thrombus formation in microvessels of the heart and lung.

Supervisor: Dr. Nadia Jahroudi

Back to Previous Page

METABOLOMICS OF WELDING FUME EXPOSURE: A NOVEL BIOMARKER APPROACH FOR MONITORING HEALTH IN WELDER APPRENTICES

Sindhu Nair, Meghan Dueck, James Mino, Marc Cassiéde, Pascal Mercier, David Broadhurst, Bernadette Quémerais, and Paige Lacy.
Supervisor: Paige Lacy

INTRODUCTION

Exposure of welders to welding fumes is a recognized occupational hazard, particularly in spaces that are poorly ventilated. Some welders develop respiratory problems that may progress into serious disease conditions such as chronic obstructive pulmonary disease (COPD). At present there are no monitoring strategies for evaluating the exposure of welders to toxic welding fumes. Metabolomics is a field of “omic” technology that serves as a powerful tool to study the changes in body fluids. Here we use this approach to determine potential biomarkers of disease associated with excessive welding fumes exposure.

METHODS

By using NMR we analyzed metabolites in human urine from male non-smoking participants (18-40 yrs) distributed into two groups: (i) 11 welders, and (ii) 6 non-welder controls with similar demographic features to the welding group. To study effects of welding fume exposure, fasting urine samples were collected on days 0, 1, 7 and 50 of the welding day program. Pooled urine was used for quality control (QC) analysis. Statistical analysis was undertaken on QC samples to filter reproducible metabolites. PLS-DA, PCA and RM-ANOVA were applied on the filtered metabolites to map differences between control and welder groups.

RESULTS

A total of 151 metabolites were identified from NMR analysis. We determined that 70 metabolites were reproducibly quantified based on QC analysis. We found that there was discrimination between welders and controls using PLS-DA analysis. RM-ANOVA on individual metabolites showed that glycine was significantly elevated in welders compared with controls on day 50 ($p < 0.05$).

CONCLUSIONS

We found some significant differences between control and welding groups in urinary metabolites. We will increase the group sizes to 20 to ensure reproducibility of our findings. This will ultimately help us to characterize biomarkers of welding fume exposure and potentially relate these to health issues in exposed welders.

Supervisor: Dr. Paige Lacy

Back to Previous Page

Pre- and post-operative prognostic value of cardiopulmonary exercise testing in liver transplant candidates: a systematic review

Ney M 1, Vandermeer B 2, Haykowsky M 3, Shah A 1, Tandon P 1
Supervisor: Dr. Puneeta Tandon

INTRODUCTION

We need better tools to predict mortality pre- and post-liver transplantation. The MELD and Child Pugh scores are limited by their liver-centric focus and inability to account for functional capacity. Cardiopulmonary exercise testing (CPET), the gold-standard measure for assessing functional capacity has shown promise as an independent prognostic tool in several large cirrhosis studies. Accordingly, we aimed to systematically review and if possible, meta-analyze studies evaluating CPET in adult patients with cirrhosis being assessed for liver transplantation.

METHODS

Inclusion criteria: i)English language, ii)100% with cirrhosis, iii)age ≥18, and iv)pre-transplant CPET testing. Studies were excluded if no clinical outcomes were reported in association with CPET testing.

RESULTS

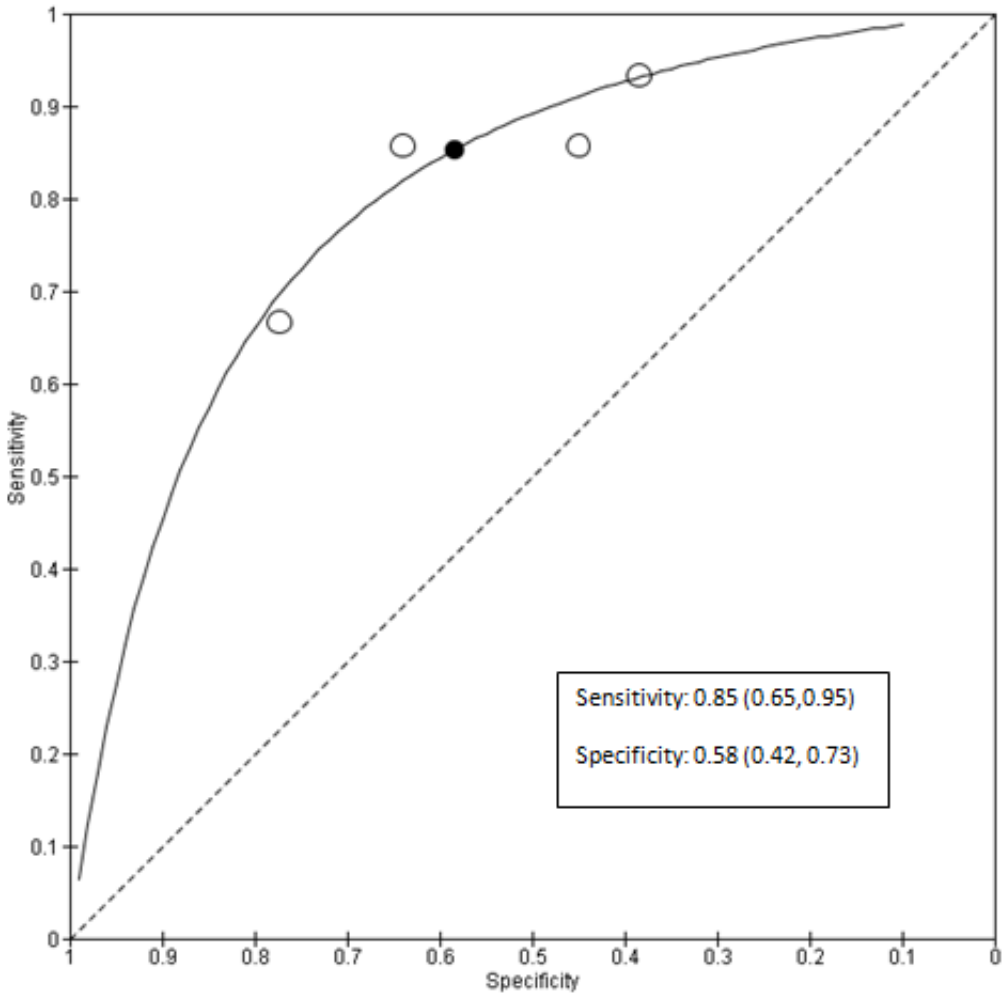
Seven studies and 1107 patients were included. Three studies reported pre-transplant mortality, all showing a significant predictive value but all using different cut-points for CPET testing. Six studies reported post-transplant mortality with heterogeneous prognostic utility. Three of the seven studies with post-transplant data were amenable to pooling to determine the diagnostic capacity of the pre-transplant peak VO2 and AT readings but were too heterogeneous for further analysis. Five of 7 studies were significant for peak VO2 as a predictor of post-transplant mortality. Three out of 4 studies assessing AT found it to be a significant predictor of post transplant mortality. The receiver operating curve analysis (ROC) of the 4 amenable studies demonstrated that peak VO2 was a sensitive (0.85, 95% CI 0.65-0.95) but not specific (0.58, 95% CI 0.42-0.73) predictor of post transplant mortality (Figure 1).

CONCLUSIONS

There is a large amount of evidence supporting the prognostic utility of CPET data to optimize the prediction of pre- and post- liver transplant outcomes. In the current analysis, peak VO2 is a sensitive but not specific marker of post-transplant mortality. High heterogeneity and variable data reporting methods prohibit a traditional pooled meta-analysis.

Supervisor: Dr. Puneeta Tandon

Back to Previous Page



Back to Previous Page

Antiviral Response of Human Mast Cells and Airway Epithelial Cells to Influenza A Exposure

Kurtis Ng, Tae Chul Moon, Harissios Vliagoftis, A. Dean Befus
Supervisor: Dr. A. Dean Befus

INTRODUCTION

The role of mast cells (MC) in host defences against influenza A virus (FluA) is poorly understood. We found that MC were resistant to productive FluA infection and could enhance the ability of airway epithelial cells (AEC) to control viral replication in co-culture systems. We hypothesized that MC interact with AEC to produce factor(s) that enhances anti-viral capabilities, therefore reducing viral replication and shedding of infectious particles and enhancing AEC survival.

METHODS

Our experimental model to investigate MC and AEC interaction during FluA infection involves a co-culture system using Transwell plates to restrict direct contact between AEC and MC. AEC (Calu-3) will be cultured on the membrane insert in the top chamber, and human MC (LAD2) in the bottom chamber. FluA strain A/PR/8/34 (H1N1) will be used. Infection (0.04 MOI [multiplicity of infection]) will be through AEC in the top chamber with an exposure period of 1 hour. Hemagglutination assay will be used to assess viral quantity. Multiplex system assay and ELISAs were used for candidate mediator detection. Commercially available antibodies are used to block the putative anti-viral activity of selected mediators.

RESULTS

2 to 4 fold reduction in viral titer in AEC-MC co-culture. Similarly, supernatant from a FluA experienced AEC-MC co-culture exhibits a protective effect against FluA in AEC. Using a candidate approach and inhibitory antibodies, AEC-MC anti-viral activity did not involve type 1 interferons or CCL-4. We are currently developing fractionation approaches to identify the MC-derived anti-viral activity.

CONCLUSIONS

Soluble factor(s) within FluA experienced co-culture supernatant have anti-viral activity against FluA infection in AEC. Identification of the anti-viral factor(s) may foster novel approaches to enhancing vaccination strategies against FluA.

Supervisor: Dr. A. Dean Befus

Back to Previous Page

The cardiac effects of deletion of adipocyte-specific ATGL.

Nirmal Parajuli1, Suresh Bairwa1, Erin Kershaw2, Jason Dyck1
Supervisor: Dyck Jason

INTRODUCTION

Heart failure (HF) induces systemic and cardiac insulin resistance and there is evidence that white adipose tissue (WAT) inflammation is involved in this process. Indeed, HF stimulates excessive WAT lipolysis (likely via enhanced beta-adrenergic drive) and this causes WAT inflammation that directly contributes to systemic insulin resistance. Although the mechanism for this is complex, recent work has shown that HF induces excessive WAT lipolysis via increased activation of adipose triglyceride lipase (ATGL; the rate-limiting enzyme involved in mediating lipolysis) and that this leads to WAT inflammation. Therefore, we hypothesize that adipocyte-specific ATGL deletion may reduce cardiac insulin resistance in HF and prevent worsening cardiac function.

METHODS

Adipose tissue-specific ATGL-deficient mice (atATGL-KO) mice were generated after crossing B6N.129-Pnpla2tm1Eek (atgl-flox) with B6N.FVB.Tg (Adipoq-Cre)1evr/J mice. Hearts were obtained from atATGL-KO.and atgl-floxed (control) mice. Protein expression was analysed by western blot technique.

RESULTS

Western blot analysis shows that NF-κβ expression is increased in WAT from mice with HF compared to controls, suggesting WAT inflammation is increased in mice with HF. In addition, hearts from atATGL-KO mice have increased insulin-dependent cardiac glucose uptake compared to controls, suggesting improved cardiac insulin sensitivity. Consistent with improved insulin sensitivity, significant down-regulation in Akt (2 fold) ($p<0.05$) was observed in hearts from atATGL-KO mice compared to controls.

CONCLUSIONS

The downregulation of phosphorylation of Akt in the hearts from atATGL-KO mice suggests that the heart and WAT communicate and that this signalling pathway plays a role in regulating cardiac insulin sensitivity. The importance of this intra-organ communication in HF is currently being investigated.

Supervisor: Dr. Dyck Jason

Back to Previous Page

Rifaximin in combination with a western-style diet induces ileal inflammation and enhances growth of Proteobacteria in IL-10-/- mice

Park, HeeKuk ; Bell, Haley ; Hotte, Naomi ; Madsen, Karen
Supervisor: Madsen, Karen

INTRODUCTION
Diet has long been considered a modulating factor in IBD due to both direct interactions with the gut mucosa and indirect effects through alteration of gut microbiota. Rifaximin is a non-systemic antibiotic used for therapy in IBD patients due to its broad anti-microbial effects. But how diet modulates host response to antibiotic treatment is not well studied. The aim of this study was to examine the effects of rifaximin therapy and a western-style diet on disease phenotypes and the gut microbiome in a mouse model of colitis.

METHODS
At weaning, IL-10-/- 129 SvEv mice were placed on chow or a western style diet high in fat (40%) and refined carbohydrate (40%) ± rifaximin (50mg/kg/day) for 35 days. Animal weight and food eaten were monitored weekly. Stool was collected for shot-gun metagenomic sequencing. Data were analyzed using Metaphlan2 and STAMP based on a total of 6,797,767 bacterial shotgun sequence reads. Plasma were measured adiponectin, resistin, insulin and glucagon using MesoScale Discovery kits. Leptin and TGFβ1 were measured using ELISA plates from R&D Biosystems.

RESULTS
In comparison with chow-fed mice, IL-10-/- mice on the western diet had increased weight gain and fat deposition. This altered composition was mirrored by changes in microbial functional pathways, with western-diet fed mice showing significantly increased microbial Galactose, glycerolipid, propionate and phosphotransferase system pathways had a direct correlation with mouse weight ($p<0.05$).

CONCLUSIONS
A western style diet alters gut microbiota and modulates inflammatory disease phenotype in a genetically-determined mouse model of colitis. Combining a western-style diet with rifaximim treatment induces a significant dysbiosis with a bloom of Proteobacteria. These findings demonstrate that the host diet and microbiome can shape both disease phenotypes and responses to antibiotic treatment.

Supervisor: Dr. Madsen, Karen

Back to Previous Page

Intra-peritoneal administration of amylin receptor antagonist, cyclic AC253, in Aβ over-expressing (TgCRND8) mice

Patel AN, MacTavish D, Soudy R, Fu W, Yang J, Westaway, D and Jhamandas JH
Supervisor: Professor Jack H Jhamandas

INTRODUCTION

Alzheimer's disease (AD) is characterized by accumulation of amyloid-β peptide (Aβ) in the brain regions that subserve memory and cognition. We have previously demonstrated that electrophysiological and neurotoxic effects of Aβ can be blocked by the amylin receptor antagonist, AC253. We have also examined the ability of chronic intracerebroventricular (icv) infusions of AC253 to restore spatial memory deficits in transgenic mice that over-express Aβ (TgCRND8).In this study, intra-peritoneal route of administration was used to study the effect of cyclic AC253 in TgCRND8 mouse model.

METHODS

Hippocampal-dependent spatial learning and memory was assessed in a standard Morris water maze (MWM). Novel object recognition was also used to study the recognition memory. Histological analyis of brain tissue was also studied for Aβ plaques and other inflammatory markers. ELISA and Western-blot were used to study total Aβ and other markers such as synapsin-1.

RESULTS

In the acquisition phase (escape latency) in MWM task, TgCRND8 mice had significantly longer escape latencies over the 7-day testing period than their respective Wt littermate controls at 3 and 6 months of age. However, TgCRND8 mice continuously injected with cyclic AC253 for a period of 10 weeks showed shorter escape latencies in MWM at later time point (i.e. at 6 months of age) compared to TgCRND8 treated with saline alone. The histological studies of brain tissue samples of these treatment groups are currently in the process.

CONCLUSIONS

These studies provide some insight into in-vivo studies for the utility of amylin receptor antagonist, cyclic AC253, in mitigating spatial memory learning deficits in a mouse model of AD.

Supervisor: Dr. Professor Jack H Jhamandas

Back to Previous Page

Clinical, Laboratory, and Treatment Outcome Characteristics of Foreign-Born Pulmonary Tuberculosis Patients in Alberta by Immigration Status, 2004-2013

Quach, K., Heffernan, C., Egedahl, M.L., Saunders, L.D., & Long, R.
Supervisor: Dr. Richard Long

INTRODUCTION

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis. Canada is a low TB incidence country, with a rate of 4.7 per 100,000 in 2013. Despite this low incidence rate, TB is found to disproportionately affect foreign-born persons from high incidence countries. This study characterizes clinical, laboratory, and treatment outcome characteristics among three groups of foreign-born pulmonary tuberculosis (PTB) patients in Alberta: Canadian citizens/permanent residents, refugees, and temporary residents.

METHODS

A retrospective cohort analysis was conducted. Inclusion criteria includes adult (age >14 years) culture-positive PTB patients classified as foreign-born and diagnosed in Alberta between 2004 and 2013. Demographic information included: age, sex, country-of-birth, time-since-arrival, and Immigration, Refugees and Citizenship Canada (IRCC) referral. Clinical characteristics included: disease type, smear status, cavitation on chest radiograph, co-presence of non-pulmonary disease, drug resistance, HIV status and treatment outcome. Statistical analysis was performed using Stata. A p-value of $<.05$ indicates statistical significance. Exploratory univariate analysis and multiple logistic regression was performed to determine if there are predictors of poor clinical, laboratory, and treatment outcome based on immigration status.

RESULTS

Overall, 646 foreign-born PTB patients were included in the analysis; 517 (80.0%) Canadian citizens/permanent residents, 30 (4.6%) refugees, and 99 (15.3%) temporary residents. Compared to Canadian citizens/permanent residents, refugees and temporary residents were more likely to be younger ($p=0.00$), recently arrived (≤2 years, $p=0.00$), and have an IRCC referral ($p=0.00$). Refugees and temporary residents were also more likely to be smear negative ($p=0.03$), drug resistant ($p=0.02$), and to have PTB alone ($p=0.02$). Treatment outcome analysis is ongoing.

CONCLUSIONS

Clinical and laboratory characteristics of foreign-born PTB patients differed by immigration status. This may have treatment outcome and programmatic implications.

Supervisor: Dr. Richard Long

Back to Previous Page

Impact of physician characteristics on outcomes in patients with heart failure

Jeyasundar Radhakrishnan, Anamaria Savu, Padma Kaul
Supervisor: Dr. Padma Kaul

INTRODUCTION

Heart failure is associated with high rates of rehospitalisation and mortality. We examined the impact of characteristics of the physician most responsible for care during a heart failure hospitalisation on mortality outcomes.

METHODS

Databases from Alberta Health were used to extract a retrospective cohort of patients with heart failure who were discharged alive after their index hospitalisation between Apr.1, 2010 and Mar. 31, 2013 with one year follow up. The physician most responsible for care during the hospitalisation was identified as the one with the most claims submitted for hospitalisation. The following physician characteristics were available: speciality (Cardiologist/Internist or other), experience level, sex, country of education, and whether the physician was fee for service or paid through an alternative payment plan. An outcome of interest was 1-year mortality. Cox regression models were used to examine the association between physician characteristics and outcomes after accounting for patient demographic and clinical factors, the later captured using the Charlson comorbidities index.

RESULTS

In total, 9422 patients (mean age 77 ± 13 and 49.5% female) were included. The 30-day mortality was 2.6% (240/9422) and at one year it was 26.2% (2465/9422). The mean age of the 1602 physicians most responsible for care during the index hospitalization was 46±8 years. Among these, 23% were Cardiology/internal medicine specialists, 73% were male, 74% had more than 10 years of experience, 41% were foreign graduates, and 19% were on an alternative payment plan. After multivariable adjustment for patient age, sex and comorbidities, physician characteristics had no impact on patient mortality outcomes (Table)

CONCLUSIONS

Physician characteristics do not appear to contribute significantly to variations in patient mortality outcomes in heart failure.

Supervisor: Dr. Padma Kaul

Back to Previous Page

Table 1 Factors Associated with One-year Mortality

Variable	1- Year Mortality OR (CI)
Patient Age (for every 10 years)	1.57 (1.50-1.64)*
Patient Sex (ref. Male)	0.84 (0.78-0.92)*
Patient Charlson Score	1.20 (1.17-1.22)*
Physician Speciality	1.08 (0.99-1.18)
Physician Age (for every 10 years)	0.91 (0.80-1.04)
Physician Sex (ref. Male)	1.04 (0.94-1.14)
Physician Experience (for every 10 years)	1.06 (0.94-1.20)
Foreign Graduate	1.03 (0.94-1.12)
Fee-for-service Physician	0.99 (0.90-1.09)

*Statistically significant at $p<0.05$, OR- Odds ratio, CI-Confidence Intervals

Back to Previous Page

Virological Footprint of T-cell Responses in Patients with Primary Biliary Cirrhosis

Mandana Rahbari 1, David Sharon 1, Amir Landi 2, Michael Houghton 2 and Andrew Mason 1
Supervisor: Dr. Andrew Mason

INTRODUCTION

Primary biliary cirrhosis (PBC) is known as a cholestatic liver disease of autoimmune origin. PBC is a disease of unknown etiology. Both genetic and environmental factors impact on the development of PBC. Our laboratory has characterized a human betaretrovirus (HBRV) in PBC patients which is highly homologous to the mouse mammary tumor virus (MMTV). Our objective is to characterize the relationship of HBRV infection with PBC. We hypothesize that patients with PBC make cellular immune responses to HBRV.

METHODS

Peripheral blood mononuclear cells (PBMCs) were purified from whole blood of 29 patients with PBC and 34 controls. T-cell responses in PBMC were assessed for reactivity to HBRV peptides. PBMCs were stimulated for 6 hours with pools of overlapping 20-mer peptides from HBRV Envelope and Gag as well as human cytomegalovirus peptides and PHA-Ionomycin mitogens, which were used as a positive control. The magnitude of ex vivo responses to stimulation were evaluated by measuring the number of T-cells secreting IL-6, IL-4, IL-10, TNF-α and IFN-γ assessed by flow cytometry.

RESULTS

38% of patients with PBC showed memory CD8+ T-cell responses to HBRV Gag peptides, whereas significantly lower number (13%) of control samples showed reactivity to HBRV Gag peptides, $p<0.04$. Out of 29 patients with PBC, 7% of patients showed memory CD8+ T-cell response to HBRV Env pool of peptides, whereas 4% of controls showed response to the stimulation with pool of HBRV Env peptides.
Despite CD8+ T-cells, memory CD4+ T-cells did not show the same level of reactivity following HBRV Gag or HBRV Env stimulation in PBC and control samples.

CONCLUSIONS

In our assay 38% of patients with PBC showed reactivity to HBRV Gag pool of peptides. Higher population of PBC patients with a CD8+ memory T-cell response to the HBRV Gag compared to the controls suggests a link between the virus and the disease.

Supervisor: Dr. Andrew Mason

Back to Previous Page

Biopsy Proven Insulitis of Clinical Islet Transplantation is not Reversed by Steroid Therapy

Behruz Rahimi, Anna Lam, Kim Solez, Patricia Campbell, Peter Senior
Supervisor: Dr. Peter Senior

INTRODUCTION

Gradual decline in islet function remains a challenge in clinical islet transplantation (CIT), but acute graft loss is relatively uncommon. Here we describe a case of acute decline in graft function with histology suggesting an immune mechanism.

METHODS

A 49 year old female (BMI 24.4 kg/m2, insulin 0.3 U/kg) with type 1 diabetes for 37 years underwent two CIT (6071 and 6827 islet equivalents/kg) following alemtuzumab induction with tacrolimus (TAC, mean 8 ug/L) and mycophenolate mofetil for maintenance. Initial engraftment was reasonable (β2 score of 12 at 1 week), but β2 score gradually declined (Fig. 1) rising to 19 after the second CIT. Insulin independence was achieved only briefly following each CIT. There was an acute decline in β2 score after day 120 (Fig. 1) prompting liver biopsy.

RESULTS

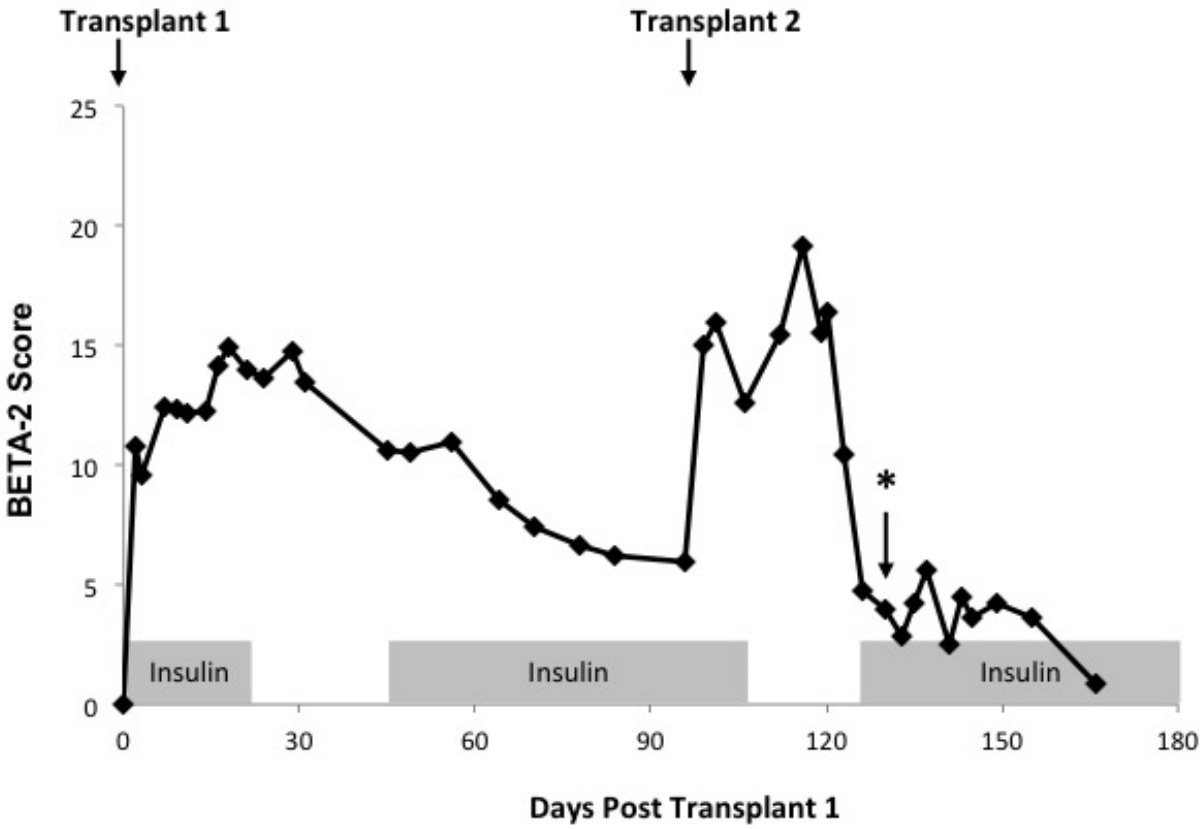
Three collections of insulin staining cells heavily infiltrated with mononuclear inflammatory cells and eosinophils were seen. TAC was increased (mean 14 ug/L) and prednisone 50 mg/day started, but graft function did not recover. Pre-CIT anti insulin antibodies were positive and anti-GAD negative, while panel reactive antibodies were 0% pre- and post-CIT.

CONCLUSIONS

This is the first report of biopsy proven insulitis post-CIT, which may be due to acute rejection and/or recurrent autoimmunity. Unfortunately, this did not reverse with steroid therapy. Further study of allo- and auto-immunity in acute CIT failure may allow targeted immune therapy.

Supervisor: Dr. Peter Senior

Back to Previous Page



Post-CIT graft function as measured by BETA-2 Score, a clinical composite score (fasting C-peptide, fasting blood glucose, insulin dose and HbA1C) after two transplants. An acute decline in graft function occurred after transplant 2, and it did not improve with treatment (*) with prednisone and increased tacrolimus dose.

Back to Previous Page

Readability of Advance Directive Forms and Health Literacy in Canada: Missing the Mark

A. Richard, W. Johnston, J. Miyasaki
Supervisor: Dr. Janis Miyasaki

INTRODUCTION

Health literacy broadly refers to the degree to which individuals have the capacity to process and understand basic health information in order to make appropriate health decisions. In the Canadian context, health literacy has been shown to depend on place of birth, education level, socioeconomic status, language spoken and geographical location. Low health literacy is associated with fewer health-promoting behaviors, poorer health status and higher rates of hospitalization and health care costs. Health literacy contributes to patient autonomy and the ability to articulate preferences and goals regarding future health care decisions. In most provinces, this requires completion of an advance directive (AD) or Goals of Care in Alberta. We hypothesize that ADs in Canada do not meet recommendations for health literacy levels.

METHODS

We obtained ADs or brochures on how to prepare an AD when an actual AD form was not available from all provinces and territories. Government websites, hospice and palliative care website were accessed to retrieve forms available to the public. Forms were then analyzed for readability using the Flesch-Kincaid scale.

RESULTS

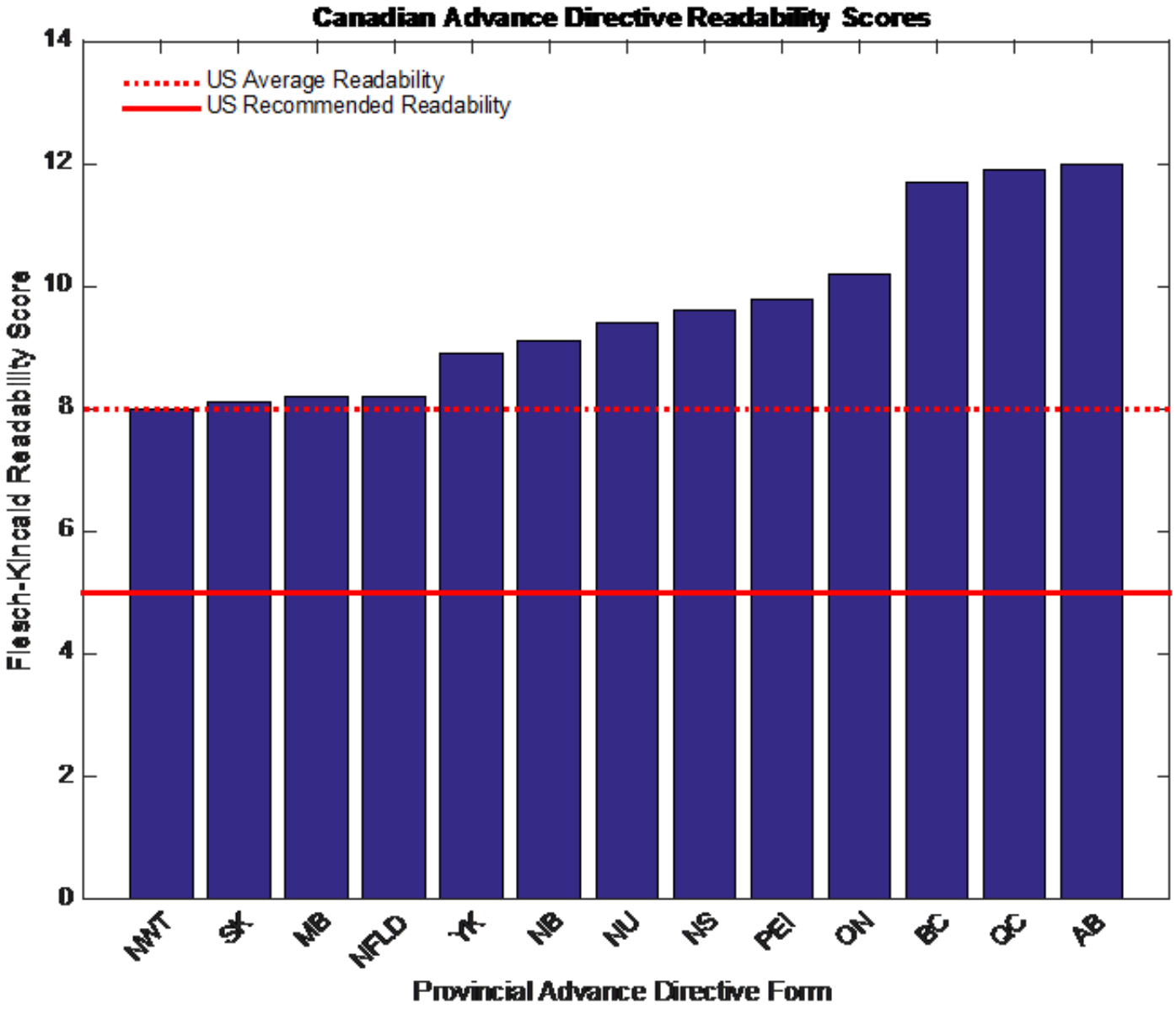
Thirteen documents were obtained and analyzed. The average Flesch-Kincaid reading level was 9.62 (median 9.40)(range 8.0-12.0). The reading level for Alberta's Goals of Care was Grade 12.

CONCLUSIONS

The National Work Group on Literacy and Health recommended a 5th grade reading level for health care documentation. All ADs documents in Canada were above the maximum recommended reading level with the highest reading levels being British Columbia, Quebec and Alberta. This indicates that Canadian AD forms may result in reduced patient autonomy. Further, governments issuing these forms have failed their fiduciary duty to citizens by producing incomprehensible forms for the most important determination in healthcare. Addressing the shortcoming among AD forms can result in increased patient engagement in AD completion and result in better delivery of care.

Supervisor: Dr. Janis Miyasaki

Back to Previous Page



Back to Previous Page

Evaluation of Patient Satisfaction With the On-TRACC Program; Benefits of a 'Joint' Approach

Investigators: Dr. Janet Roberts, Dr. Stephanie Keeling, Dr. Steven Katz

BACKGROUND:

Rheumatoid arthritis (RA) is a chronic disease that impacts all facets of the lives of those diagnosed. Given the potential impairment and disability from poorly-controlled disease, aggressive disease control is critical. Management by an interdisciplinary team, a concept employed in the treatment of many chronic diseases, leads to a holistic model of healthcare delivery, which may result in better outcomes for the patient. The University of Alberta Division of Rheumatology has launched a new multidisciplinary clinic, the On-TRACC Program (On Treating Rheumatoid Arthritis – Providing Access to Care), which provides aggressive disease modification, co-morbidity management in a shared-care model of rheumatologists and advanced care practitioners.

OBJECTIVES:

To evaluate patient satisfaction in patients enrolled in the On-TRACC program compared to those treated in general rheumatology clinics through a patient satisfaction survey.

METHODS:

We performed an observational cross-sectional survey study using a modified version of the Leeds Satisfaction Questionnaire, a validated and reliable tool developed for RA outpatient clinics, to compare satisfaction between the two patient groups: On-TRAAC and the traditional model of care (TMC). The six groups included in the questionnaire's subscales, and thus assessed with this survey included: (1) provision of information, (2) empathy with the patient, (3) attitude to the patient, (4) access to and continuity with the caregiver, (5) technical competence and (6) overall satisfaction. A sub-group analysis of patient satisfaction between the first and subsequent visit in the On-TRACC group was also performed.

RESULTS:

A total of 47 patients completed the survey (23 patients in the On-TRAAC group and 24 in the TMC). The average age of the participants was 54 years and included 12 males and 36 females. The overall satisfaction score was 4.35 in the TMC group and 4.44 in the On-TRAAC group (higher value represents higher satisfaction). Ten patients in the On-TRAAC group performed the survey at least twice and showed an overall trend towards improved satisfaction on subsequent visits with an initial overall satisfaction score of 4.48 and follow up score of 4.55.

CONCLUSION:

While patients in both treatment groups were very satisfied with their care, there is a trend towards improved satisfaction with the multi-disciplinary care model. Larger patient numbers are needed to provide meaningful comparisons between these different models of care.

Back to Previous Page

Early programming of glucose metabolism among children with obesity born from complicated pregnancies

Christian F. Rueda-Clausen, MD, PhD, FTOS 1,2, Alanna Friense1, Raj S. Padwal MD MSc FRCPC1,2 Arya M. Sharma MD PhD FRCPC 1,2 Kathryn A. Ambler, MSc3 & Geoff D.C. Ball, PhD, RD2,3
Supervisor: Raj Padwal, Arya Sharma

INTRODUCTION

Emerging evidence suggest that variability in the presentation of obesity-related cardiometabolic risk factors could be influenced by exposure to certain factors during crucial periods of development, a phenomenon known as fetal programming. We hypothesized that children with obesity who were born from complicated pregnancies would exhibit obesity-related cardiometabolic risk factors.

METHODS

This case-cohort study, which included information from a clinical database of children with severe obesity who were enrolled in a publically funded multidisciplinary, tertiary-level weight management clinic (Edmonton, Canada) between April of 2005 and May of 2012. Clinical data at time of enrolment were complemented with perinatal information obtained by reviewing both maternal and children's perinatal medical records. Associations between perinatal events (e.g., intrauterine growth restriction, gestational diabetes, pregnancy induced hypertension) and the presence of obesity-related cardiometabolic risk factors were estimated.

RESULTS

Maternal and neonatal medical records from 152 children with obesity (51% male; mean age 10.4±2.2 y; mean BMI-z score= 3.23±0.7 WHO-2007 reference) were included in the analyses. Most prevalent cardio metabolic risk factors in children included impaired glucose metabolism (IGM: 54.2%), dyslipidemia (42.6%), and increased blood pressure (26.6%). Perinatal events that were associated with the presence of IGM included (prevalence, OR [95%CI]): gestational diabetes (14.5%, 4.1 [1.3,13.0]), maternal smoking (28.9%, 2.3 [1.0,5.2]), and maternal weight gain below target (21.1%, 3.5[1.3,8.9]). Dietary fiber intake, physical activity, and central adiposity are strong and consistent confounders of these associations. Maternal BMI at baseline and weight gain during pregnancy exert independent and synergistic associations with obesity-related impaired glucose metabolism in children.

CONCLUSIONS

A clinically relevant association exists between perinatal events and identification of cardiometabolic risk factors in children with obesity. Our observation that behavioral parameters influence this relationship suggests that diet and physical activity-related variables might function as therapeutic targets to modify cardiometabolic risk in children with obesity who were born from complicated pregnancies.

Back to Previous Page

Comparison of Quantum Blue Rapid Test versus Fecal Calprotectin ELISA as a Non-invasive Marker to Predict Colonic Inflammation in Ulcerative Colitis

Silva M, Valcheva R, Hassanzadeh Keshteli A, Hoevers T, Dieleman LA
Supervisor: Dr. Levinus Dieleman

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease including Crohn's disease and ulcerative colitis (UC). Current standard practice in determining relapse is symptoms-based combined with invasive colonoscopy. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are non-invasive serum markers of inflammation, however they are neither specific nor sensitive. Fecal calprotectin (FCP) is a 36.5 kD non-glycosylated human protein released during intestinal inflammation, with FCP of >200mg/l being highly associated with endoscopic inflammation. Currently FCP can be measured using ELISA with a turn-around time of 14 days or using the 24-48 hours Quantum Blue rapid test. The aim of this study is to compare fecal calprotectin values between ELISA versus Quantum Blue rapid test as biomarkers of endoscopic relapse of ulcerative colitis.

METHODS

Stool samples from 19 ulcerative colitis patients from the IBD Clinic at University of Alberta were homogenized in Extraction buffer (1:50 weight/volume). These homogenates were used both in ELISA and Quantum Blue FCP assessments (Bühlmann Laboratories AG).

RESULTS

Pearson correlation analysis showed a statistically significant correlation between ELISA and Quantum Blue rapid tests ($r=0.87$, $p < 0.001$). However, the Quantum Blue test likely underestimated colonic inflammation (defined as FCP of >200 mg/l per ELISA test) in ulcerative colitis. A ROC curve analysis to define a cutoff value for the Quantum Blue rapid test based on using ELISA as a gold standard was 154 (sensitivity 85.7%, specificity 100%).

CONCLUSIONS

Despite a high correlation of FC results between the Quantum Blue rapid and ELISA tests the rapid test will likely underestimate UC patients who have colonic inflammation versus the relatively slow ELISA test. A lower cut-off value of 154 to predict colonic inflammation is suggested for the Quantum Blue rapid test in order to increase its sensitivity.

Supervisor: Dr. Levinus Dieleman

Back to Previous Page

Extrapolation of sensory data into a pain score

F.J. Slomp1, M.J. Mayan2, G.C. Lasiuk3 and B.Dick
Supervisor: Dr. Bruce Dick

INTRODUCTION

Pain is a complex phenomenon that affects physical, mental and emotional experience. The numeric rating score (NRS) is commonly used to elicit a pain score. It is this pain metric that functions as the bridge between the subjective (experience) and objective (pain management); therefore it is central to pain management. However, health care practitioners (HCPs) are somewhat hesitant about the NRS's clinical trustworthiness. It has been assumed that individuals can individuals interpret and extrapolate pain related information to provide a "pain score" but there is very little evidence to substantiate this claim. The purpose of this research was to determine how an individual reduces the myriads of experiential information to elicit a pain score.

METHODS

Following the approach of Interpretive Description described by Thorne and colleagues, 13 participants were purposefully recruited for a study of how people evaluate their acute pain in order to provide a numerical "pain score" for HCPs. Data collection involved semi-structured interviews and analysis was simultaneous and iterative.

RESULTS

Participants described "receiving an injury", "sensing the imminent loss of consciousness" (ILC) and "grasping the immediate context" as the experiential referents they employed to derive a pain score. Participants operationalized the scale and used the ILC as the scale's anchor rather than the scale anchor provided by HCPs.

CONCLUSIONS

People with acute physical trauma, interpret and extrapolate multiple sensory data in a systematic fashion to derive a "pain score". The use of the ILC as the anchor for the NRS has important implications for the effective assessment and treatment of acute pain management.

Supervisor: Dr. Bruce Dick

Back to Previous Page

IDENTIFICATION OF SHORT BRAIN PENETRANT AMYLIN RECEPTOR BASED PEPTIDES AS NOVEL THERAPEUTICS FOR ALZHEIMER'S DISEASE

Rania Soudy1, Wen Fu1, Kamaljit Kaur2, Jack Jhamandas1
Supervisor: Dr. Jack Jhamandas

INTRODUCTION

Aggregation and deposition of β-amyloid (Aβ) peptides in brain play a pivotal role in Alzheimer's disease (AD) pathogenesis.We have identified the amylin receptor as a putative target for the deleterious effects of Aβ in the brain, and AC253 peptide (24 amino acid), an amylin receptor antagonist, restores spatial memory and learning in in vitro and in vivo experimental paradigms of memory and AD. Identification of shorter amylin receptor antagonist peptides will facilitate its translation to clinical trials.

METHODS

A peptide library of 14 peptide fragments synthesized on cellulose membrane was screened for binding to amylin receptor using transfected HEK-293 (AMY3)-expressing cells. Promising sequences were synthesized using Fmoc synthesis, and labeled wth cy5.5 dye for further studies. In vitro cell uptake was evaluated in AMY3 cells using flow cytometry and fluorescence microscopy. Ex-vivo brain uptake was done using near infrared imaging, and fluorescence microscopy.

RESULTS

Peptides R5(12 aa), and R14 (14 aa) showed significant binding to HEK293-AMY3 cells compared to other library fragments. In vitro studies showed that both peptides blocked human amylin cellular responses in HEK293-AMY3 cells with equal the potency as full length AC253. In vitro flow cytometry and fluorescence microscopy cell uptake studies demonstrated that R5, and R14 peptides have selective and significant specific binding to HEK293-AMY3 cells similar to AC253. Ex vivo brain imaging in wild type mice after (ip) administration of cy5.5 labelled peptides revealed that both R5, and R14 peptides can cross the BBB, and peptide R5 showed superior brain penetration to that observed in AC253. Microscopy studies showed that the lablled peptides were mainly distributed in the hippocampal and cortical regions, which coincides with the amylin receptor localization in the brain.

CONCLUSIONS

Our data identify novel promising peptides amylin receptor antagonists for future pre-clinical and clinical studies in AD, and they can be used for enhanced drug delivery over the BBB.

Supervisor: Dr. Jack Jhamandas

Back to Previous Page

Distinguishing cardiac Troponin fragment sizes in patients with type 1 vs type 2 myocardial infarction

Somaya Zahran, Vivian Figueiredo, George Cembrowski, Michelle Graham, Richard Schulz, Peter Hwang
Supervisor: Hwang, Peter

INTRODUCTION

Myocardial infarction (MI) afflicts more than 70,000 Canadians each year. There are two common types: type 1 MI is caused by acute cholesterol plaque rupture and clot formation occluding a coronary artery, while type 2 MI is caused by an imbalance between cardiac blood supply and demand. It is vitally important to distinguish between the two because the treatments are drastically different.
The gold standard for diagnosing MI is the serum cardiac troponin test. While it is known that cardiac troponin I (cTnI) is readily degraded in myocardial ischemia, it is unknown whether there is a difference in the degree of degradation in type 1 versus type 2 MI.

METHODS

We collected blood samples from 22 patients with type 1 MI and 21 patients with type 2 MI. All type 1 patients had their diagnosis confirmed by angiography. The type 2 patients were determined to be such based on their clinical history.
The blood samples were tested against a series of sandwich ELISA- (enzyme-linked immunosorbent assay)-based tests, using commercially available antibodies for cTnI. The capture antibody (19C7) recognizes a cTnI epitope from its well-structured core, while the detection antibodies target either the structured core (antibody 560), intrinsically disordered N-terminal region (M18), or C-terminal region (MF4).

RESULTS

All three capture-detection antibody pairings were able to detect cardiac troponin I in patient samples. However, some patient samples yielded significantly higher readings for the 19C7-M18 antibody pairing, while others yielded higher readings for the 19C7-MF4 pairing.

CONCLUSIONS

Preliminary analysis suggest that there is no difference in the proteolytic degradation of cardiac troponin I in type 1 MI versus type 2 MI patients. Further analysis is needed to determine if the different detection rates observed in this study correlate with clinically relevant parameters like time since symptom onset, angiography results, time before/after revascularization, and troponin level.

Supervisor: Dr. Hwang, Peter

Back to Previous Page

Microtubule acetylation facilitates intracellular communication: a new mitochondria-to-nucleus “highway”

Zervopoulos SD, Boukouris AE, Haromy A, Kinnaird A, Gurtu V and Michelakis ED
Supervisor: Dr. Evangelos Michelakis

INTRODUCTION

Microtubules form a dynamic cytoplasmic network. Acetylation of α-tubulin promotes microtubule stability, critical for intracellular trafficking, and regulated by α-tubulin acetyltransferase 1 (αTAT1) versus histone deacetylase 6 (HDAC6). The mitochondrial pyruvate dehydrogenase complex (PDC) translocates to the nucleus and produces acetyl-CoA for histone acetylation required for proliferation (Cell 2014). The mechanism for this translocation remained unclear. We hypothesized that microtubule acetylation facilitates either mitochondrial translocation around the nucleus (where they can directly “donate PDC”) or the trafficking of PDC-containing vesicles/endosomes toward the nucleus.

METHODS

We used A549 cancer cells under proliferative signals (hypoxia, serum) and tubacin (an HDAC6 inhibitor) vs αTAT1 siRNA. We measured nuclear PDC (immunoblots, confocal microscopy), tubulin acetylation (immunoblots) and mitochondrial traficking (confocal and electron microscopy in fixed and live cells utilizing a mitochondria-targeted photoactivatable GFP).

RESULTS

Hypoxia and serum increased tubulin acetylation, perinuclear mitochondrial clustering and nuclear PDC. Hypoxia also increased nuclear PKM2, a cytoplasmic glycolytic enzyme which, like PDC, has been described in cancer. Hypoxia increased mitochondrial perinuclear clustering exhibiting a sliding “kiss-and-run” pattern around the nuclear membrane. Tubacin increased both tubulin acetylation and nuclear PDC under hypoxia and serum stimulation, but did not affect mitochondrial clustering. In contrast, αTAT1 silencing decreased tubulin acetylation and nuclear PDC under hypoxia but not serum. Both interventions did not affect nuclear PKM2 levels.

CONCLUSIONS

Our data suggest the presence of two pathways for nuclear translocation of mitochondrial proteins. One microtubule-independent mechanism involving direct “donation” of PDC to the nucleus potentially by fusion of nuclear/mitochondrial membranes (similar to how mitochondria fuse to ER membranes). And another, regulated by tubulin acetylation, particularly in hypoxia, involving mitochondrial but not cytoplasmic proteins. Translocation of metabolic enzymes to the nucleus provides the basis of the newly discovered metabolism-epigenetics axis and elucidation of specific regulatory mechanisms will facilitate novel drug development in cancer and beyond.

Supervisor: Dr. Evangelos Michelakis

Back to Previous Page

Does a transition service reduce ALC days and total non-acute-care days for stroke patients in Alberta?

Yufei Zheng
Supervisor: Dr. Philip Jacobs

INTRODUCTION

Stroke patients may require rehabilitation or other post-acute care after acute hospitalization. Due to the non-availability of post-acute beds, patients may remain waiting in acute care and be designated to be at an Alternate Level of Care (ALC). To effectively reduce ALC days, lower intensity transition services are provided in several hospitals. We studied whether transition services reduced ALC days and the non-acute LOS for stroke patients.

METHODS

We selected stroke patients with an index admission between 2004 and 2013. We limited the study to stroke patients admitted to a rehabilitation hospital in Calgary (with transition service) or in Edmonton (without transition service). The acute care episode starts from the initial admission to an acute hospital and ends when the patients were designated to ALC or transferred to other hospitals. The ALC days are the total ALC days during the acute care episode. The length of stay of the non-acute-care stage is the sum of ALC days and the non-acute LOS.
We used a two-part model for the analysis of ALC days and a generalized linear model for the study of acute and total non-acute-care LOS. Propensity scores were applied to adjust for imbalances of patient characteristics.

RESULTS

Among 2,961 patients (44.9% in transition service), 35.8% had ALC stay (mean=4.3, SD=8.5 days). On adjusted analysis, the patients with transition service had -5.7 (95%CI= -8.0 ~ -3.4) less ALC days, but the non-acute care LOS including rehabilitation was the same in both settings. However, acute care LOS was -1.0 days (not significant) shorter in the transition service setting.

CONCLUSIONS

The transition service slightly reduced acute LOS and ALC days for stroke patients but did not impact the total non-acute LOS. Transition services could potentially reduce cost and maximize time in post-acute care by reducing time that stroke patients are in acute care hospitals.

Supervisor: Dr. Philip Jacobs

Back to Previous Page