Chair's Welcome

Barbara J. Ballermann, MD

"Welcome to our Research Day - one of the most important and rewarding days in our academic year! It is a day when we hear about the exciting research projects in which our Graduate Students, Post Doctoral Fellows, Core Internal Medicine and Subspecialty Residents are involved. This year we are fortunate to have as our guest oral adjudicator, Dr Peter Paré, Professor of Medicine and Pathology, Faculty of Medicine from the University of British Columbia.

Research Day gives the opportunity for all Department members and guests to interact with our young researchers. As such, I would encourage you to attend the oral presentations in Classroom D and visit at least three posters which will be located in the lower level of the John W Scott Library.

Enjoy today and be sure to join us for the presentation of awards at the conclusion of the afternoon oral presentations."

IN LIEU OF AN INTRODUCTION FROM
EVANGELOS MICHELAKIS, MD, ASSOCIATE CHAIR, RESEARCH:

ITHAKA

As you set out for Ithaka
hope the voyage is a long one,
full of adventure, full of discovery.
Laistrygonians and Cyclops,
angry Poseidon—don't be afraid of them:
you'll never find things like that on your way as long as you keep your thoughts raised high, as long as a rare excitement stirs your spirit and your body.
Laistrygonians and Cyclops,
wild Poseidon—you won't encounter them
unless you bring them along inside your soul, unless your soul sets them up in front of you.

Hope the voyage is a long one.
May there be many a summer morning when, with what pleasure, what joy, you come into harbors seen for the first time; may you stop at Phoenician trading stations to buy fine things, mother of pearl and coral, amber and ebony, sensual perfume of every kind— as many sensual perfumes as you can; and may you visit many Egyptian cities to gather stores of knowledge from their scholars.

Keep Ithaka always in your mind.
Arriving there is what you are destined for.
But do not hurry the journey at all.
Better if it lasts for years,
so you are old by the time you reach the island, wealthy with all you have gained on the way, not expecting Ithaka to make you rich.

Ithaka gave you the marvelous journey.
Without her you would not have set out.
She has nothing left to give you now.

And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience, you will have understood by then what these Ithakas mean.

CP CAVAFY ~1919

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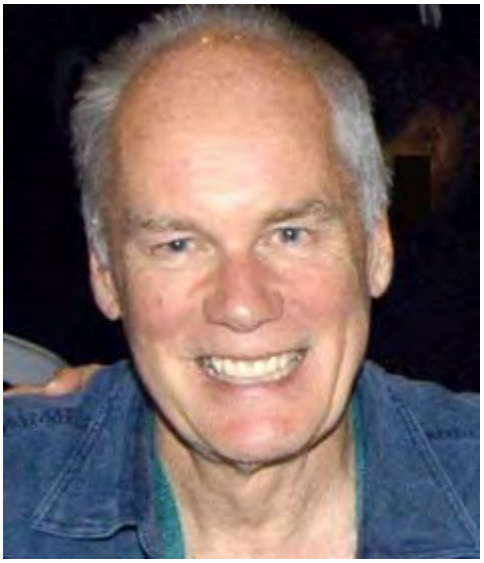
Research Day Guest Adjudicator

Peter David Paré, MD



Dr. Peter D. Paré's research expertise is in the study of the physiological assessment, pathophysiology and more latterly the genetics of asthma and chronic obstructive pulmonary disease.

He earned his medical degree from McGill University in Montreal in 1969. His residency training was done at the Royal Victoria Hospital and the University of Nairobi before completing a two year postdoctoral fellowship at the Meakins Christie Laboratories.

Dr. Peter D. Paré is currently Professor of Medicine and Pathology in the Faculty of Medicine at the University of British Columbia. He was the division head and training program director of the UBC respiratory division between 1983 and 1994. He was director of the The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research at St Paul's Hospital (1998-2005) and Program Director of the Clinical Investigators Program for the Faculty of Medicine at UBC. He is the recipient of the Jacob Churg Distinguished Researcher award and a Michael Smith Distinguished Scholar, Michael Smith Foundation for Health Research.

Panel of Judges

Peter Paré, MD
Professor of Medicine and Pathology
Faculty of Medicine
University of Brisith Columbia

Barbara J. Ballermann, MD
Professor of Medicine
Chair, Department of Medicine
University of Alberta

Paul W. Armstrong, MD
Distinguished University Professor – Medicine (Cardiology)
Director, Canadian VIGOUR Centre,
University of Alberta

Morning Session Chair

Dr. Ross Tsuyuki
Co-Director, Graduate Education Program

Afternoon Session Chair

Dr. Darryl Rolfson
Director, Postgraduate Medical Education

Meeting at a Glance

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Graduate Students & Post Doctoral Fellows
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Oral Presentations
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Scoring Criteria
Oral Presentation

♦	Innovation	/2
♦	Quality of Data	/4
♦	Clarity & Style of Presentation	/2
♦	Quality of Discussion - Response to questions	/2
♦	**OVERALL RATING**	/10

Scoring Criteria
Poster Presentation
(1=Poor, 5=Excellent)

Clarity & justification of the research question	1 2 3 4 5
Clarity of the working hypothesis	1 2 3 4 5
Appropriateness of the methods used to answer the hypothesis	1 2 3 4 5
Validity & relevance of the results to the hypothesis	1 2 3 4 5
Quality of the discussion & conclusion(s)	1 2 3 4 5
Visual layout & visual impact	1 2 3 4 5
Oral response to adjudicators' questions	1 2 3 4 5
TOTAL SCORE	_____ **35**

Pinprick test in Small Fiber Neuropathy: Accuracy and pitfalls

Derrick Blackmore, BSc

University of Alberta Hospital, Edmonton, AB, Canada

INTRODUCTION: Painful small fiber sensory neuropathy (SFN) is a relatively common disabling medical condition, which exclusively or predominantly affects the A-δ (small myelinated) and nociceptive C (unmyelinated) nerve fibers and their functions. Patients with SFN frequently have burning ("feet are on fire"), sharp ("knife-like, jabbing or pins and needles"), shooting, and aching pain in the toes and feet. Depressed perception of pinprick sensation on neurological examination is frequently cited as diagnostic criteria for SFN, though the sensitivity, specificity and correlation of this clinical tool with laboratory tests of small nerve fiber function have not been well evaluated. **METHODS**: We assessed the sensitivity, specificity and predictive value of pinprick perception in a large cohort of patients as measured by concordance with established laboratory measures of small fiber function. All patients suspected to have SFN underwent detailed neurologic evaluation, including documentation of their clinical history and neurological examination by an independent neurologist and underwent standardized quantitative sensory and autonomic testing. **RESULTS**: Sensitivity, specificity and predictive values of pinprick perception were relatively consistent between modalities. The diagnostic yield was increased by combining the number of modalities used. Overall, pinprick sensitivities were equivocal, but predictive values differed considerably. In our cohort the positive predictive value (PPV) of pinprick testing on clinical exam approached 89% when testing modalities were combined; however, the negative predictive value was considerably lower (19%). **CONCLUSIONS**: We conclude that as an independent screening tool, pinprick sensitivity has

only a moderate sensitivity in identifying SFN. Although the positive predictive value is high, it is likely that many patients with SFN may be missed if the subjective perception of the pinprick sensation is not found to be impaired. Our findings indicate that wherever clinically indicated, multimodal testing be performed to positively rule out the diagnosis of SFN. **SUPERVISOR**: Zaeem A. Siddiqi, MD, PhD.

The Role of p53 in Cancer Angiogenesis

Haromy A, Sutendra G, Dromparis P, Bowers L, Hashimoto K, McMurtry MS and Michelakis ED

BACKGROUND: Cancer angiogenesis is essential for tumor progression and metastasis. Loss of function of the redox-sensitive transcription factor and tumor suppressor protein p53 occurs in approximately 50% of all cancers. Mitochondria are important oxygen sensors and p53 regulates mitochondrial function and could modulate hypoxic/HIF1α (hypoxia inducible factor 1α) signaling. We hypothesize that activation of p53 decreases cancer angiogenesis.

METHODS/RESULTS: We used two human mammary carcinoma cell lines expressing low ($p53^{Low}$) and high ($p53^{High}$) p53 levels (qRT-PCR, immunofluorescence). At baseline, $p53^{Low}$ cells had significantly decreased p53 activity (assessed by nuclear localization using immunofluorescence and expression of the p53 target genes-p21, MDM2 and PUMA) compared to $p53^{High}$ cells. HIF-1α expression (qRT-PCR) and activity (nuclear localization; immunofluorescence) was significantly increased in the $p53^{Low}$ compared to the $p53^{High}$ cells. The HIF-1α regulated genes encoding for glucose transporters-1,3 and 4 were increased in $p53^{Low}$ compared to the $p53^{High}$ cells. To assess the role of p53 in angiogenesis *in-vitro*, we used a matrigel assay. Similar to hypoxia (a standard model used to promote angiogenesis), preconditioned media from $p53^{Low}$ cells significantly increased angiogenesis (tubule formation) in normoxic human aortic endothelial cells compared to preconditioned media from $p53^{High}$ cells.

CONCLUSION: In addition to its tumor suppressing function, p53 is important in inhibiting angiogenesis by decreasing the expression and activity of the pro-angiogenic transcription factor HIF-1α.

Oral iron replacement is associated with a significant reduction in gut microbial biodiversity in iron deficient inflammatory bowel disease (IBD) patients

Lee TW, Foshaug R, Hotte N, Dieleman LA, Sadowski D, Madsen K, Fedorak RN

Background: Iron deficiency is common in patients with Inflammatory Bowel Disease (IBD) and iron replacement can occur orally or intravenously. Previous studies indicated oral iron therapy may exacerbate IBD but the precise mechanism is unknown. Given the role of intestinal bacteria in the pathogenesis of IBD, we hypothesized this injurious effect of oral iron may occur as a consequence of altered colonic microbiota. We aim to describe the microbiota composition of iron deficient patients receiving either oral or intravenous iron replacement therapy and correlated these changes with clinical disease activity index.

Methods: Patients with iron deficiency and not on iron replacement were randomized to either intravenous or oral iron replacement. Stool and sigmoid mucosal biopsies were collected prior to iron replacement and at 3 months. Terminal Restriction Fragment Length Polymorphism (TRFLP) analysis was performed to analyze the faecal and mucosal microbiome. Disease activity index for Crohn's disease and ulcerative colitis were determined at baseline and after 3 months of iron therapy.

Results: Results from 16 IBD patients were analyzed (10 female, 6 male). After 3 months of oral iron treatment, a statistically significant reduction in the colonic microbiome biodiversity was seen compared to baseline ($p = 0.017$). This reduction in biodiversity with oral iron occurred as a consequence of compositional changes within the phyla Firmicutes and Proteobacteria. There was no significant change in the colonic microbiome biodiversity with intravenous iron replacement ($p=0.933$). No worsening of disease activity was noted with either route of iron therapy.

Conclusions: This is the first study to demonstrate that oral iron replacement therapy in patients with IBD is associated with compositional changes of the colonic microbiota and a significant reduction of its biodiversity. Iron therapy did not exacerbate inflammatory bowel disease clinical disease activity.

A Validation Study of Endoscopy And Confocal Endomicroscopy In a Mouse Model of Colitis

Rae R Foshaug, Aducio Thiesen, Karen Kroeker, Thomas Lee, Karen Wong, Julia Liu, Karen Madsen, Richard N Fedorak

Introduction: In mouse models of inflammatory bowel disease intestinal injury is generally assessed using various clinical parameters and histological scoring. Novel imaging modalities allow for the real-time viewing of intestinal injury in vitro. We have adapted a flexible urethra-endoscope (Olympus Canada Inc.) for high resolution video endoscopy and monitoring of intestinal disease progression in living mice and have coupled this video endoscopy with confocal endomicroscopy (OptiScan 5), allowing for correlation between endoscopic findings and 3-dimensional imaging. This project correlates and validates images obtained through endoscopy and confocal endomicroscopy with disease onset and progression in a mouse model of colitis.

Methods: Colitis was induced in 9 week old male 129/SvEv mice by the addition of 5% dextran sodium sulfate (DSS) into the drinking water for 7 days and then returned to regular water for an addition 7 days of recovery. Clinical disease was assessed by measurement of body weight, stool consistency, and presence of blood. Mice were studied at days 0, 3, 6, 9, 12 and 15 days. Using a ketamine-cocktail anesthesia, mice were subjected to endoscopy ~6cm into the distal colon at each experimental timepoint. Immediately following endoscopy, confocal endomicroscopy was done using acroflavin stain on a section of colon undisturbed by endoscopy (~7cm). Mice were then euthanized via cervical dislocation and colonic tissues collected for histology, and analysis of microflora using fluorescence in situ hybridization (FISH). Digital images from endoscopy and confocal endomicroscopy were assigned a colitis score by three independent viewers.

Results: Endoscopic images over the time course 0-15 days showed clear evidence of disease progression, with early loss of vasculature followed by ulcer formation and overt bleeding. Colitis scores (0-2) from the three reviews yielded a Kappa value of 0.733. Confocal endomicroscopy revealed loss of surface epithelial cells, more widely spaced crypts and focal crypt destruction. Disease injury scores obtained by confocal endomicroscopy (0-3) also correlated closely with endoscopy scores. FISH analysis showed a clear distortion of microflora colonization starting at day 6 and becoming evident by day 9. Further analysis of bacterial presence is in progress.

Conclusion: Through the adaptation of human endoscopy into a mouse model, a visual image can be obtained to determine various physical markers of disease over a time course ultimately reducing the number of animals required in experiments.

LONG-CHAIN INULIN AND SHORT-CHAIN FRUCTO-OLIGOSACCHARIDES HAVE DIVERGENT EFFECTS ON INTESTINAL MICROBIOTA AND COLITIS REDUCTION IN HLA-B27 TRANSGENIC RATS

Petya T. Koleva[1,2], Rosica S. Valcheva[1], Michael G. Gänzle[2], Levinus A. Dieleman[1]

[1]Centre of Excellence for Gastrointestinal Inflammation and Immunity Research, [2]Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada

Introduction: Modification of the intestinal microbiota may restore the balance of the host bacteria and reduce inflammation in Inflammatory Bowel Disease (IBD). Non-digestible fermentable carbohydrates can stimulate the growth of specific protective intestinal bacteria. We reported that a combination of inulin and fructo-oligosaccharides (FOS) reduced colitis in HLA-B27 transgenic (TG) rats. Inulin and FOS are linear β (2→1) linked fructans with different degree of polymerisation. The aim of this study was to compare the effects of long-chain inulin versus short-chain FOS on colitis reduction and the composition of gut bacteria in this IBD model.

Methods: HLA-B27 TG rats were fed inulin, FOS, or not, for 12 weeks. Fecal samples were collected at four weeks of age, cecal and fecal samples were collected at necropsy at sixteen weeks. Inflammation was assessed using a validated histology score and by quantification of intestinal IL1-β concentration. The intestinal microbiota was analyzed using quantitative PCR employing group-specific primers.

Results: Both inulin and FOS reduced colitis. However, inflammation in FOS-treated animals was less severe compared to inulin-treated animals. Fructans had divergent effects on intestinal microbiota. FOS increased fecal *Bifidobacterium* spp., *Bacteroides* group and *Enterobacteriaceae* spp., whereas inulin stimulated fecal *Clostridium* cluster XIVa. Both inulin and FOS increased fecal *Lactobacillus* spp. and *Clostridium* cluster I. Linear discriminant analysis showed that FOS-fed animals were well-separated from clusters representing inulin-fed and control animals for both cecal and fecal samples. The analysis confirmed that inulin and FOS resulted in divergent effects on cecal and fecal microbiota.

Conclusions: The degree of polymerization of prebiotics determines colitis reduction and the effects on the cecal and fecal microbiota in HLA-B27 TG rats. Such effects need to be taken into account when developing therapeutic trials using prebiotics in IBD.

Supervisors: Drs. Michael Gänzle and Levinus Dieleman

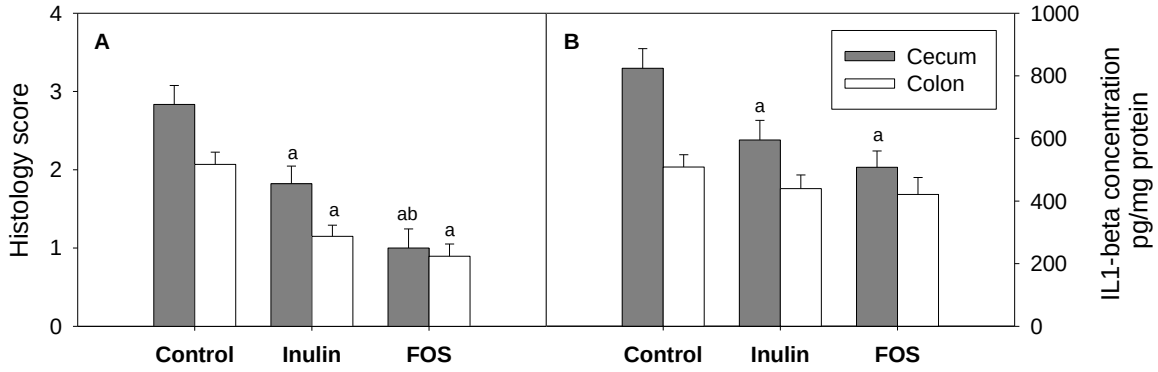

Figure 1. Histology score (A) and IL-1β concentration (B) of cecal and colonic tissue samples collected from HLA-B27 transgenic rats. The rats were either treated with inulin or oligofructose, or not. The statistically significant differences ($P \leq 0.05$) between control diet and fructo-oligosaccharide (FOS) treatments are indicated with 'a', whereas 'b' demonstrates significant difference between inulin versus FOS. Results are expressed as least-square mean ± SEM.

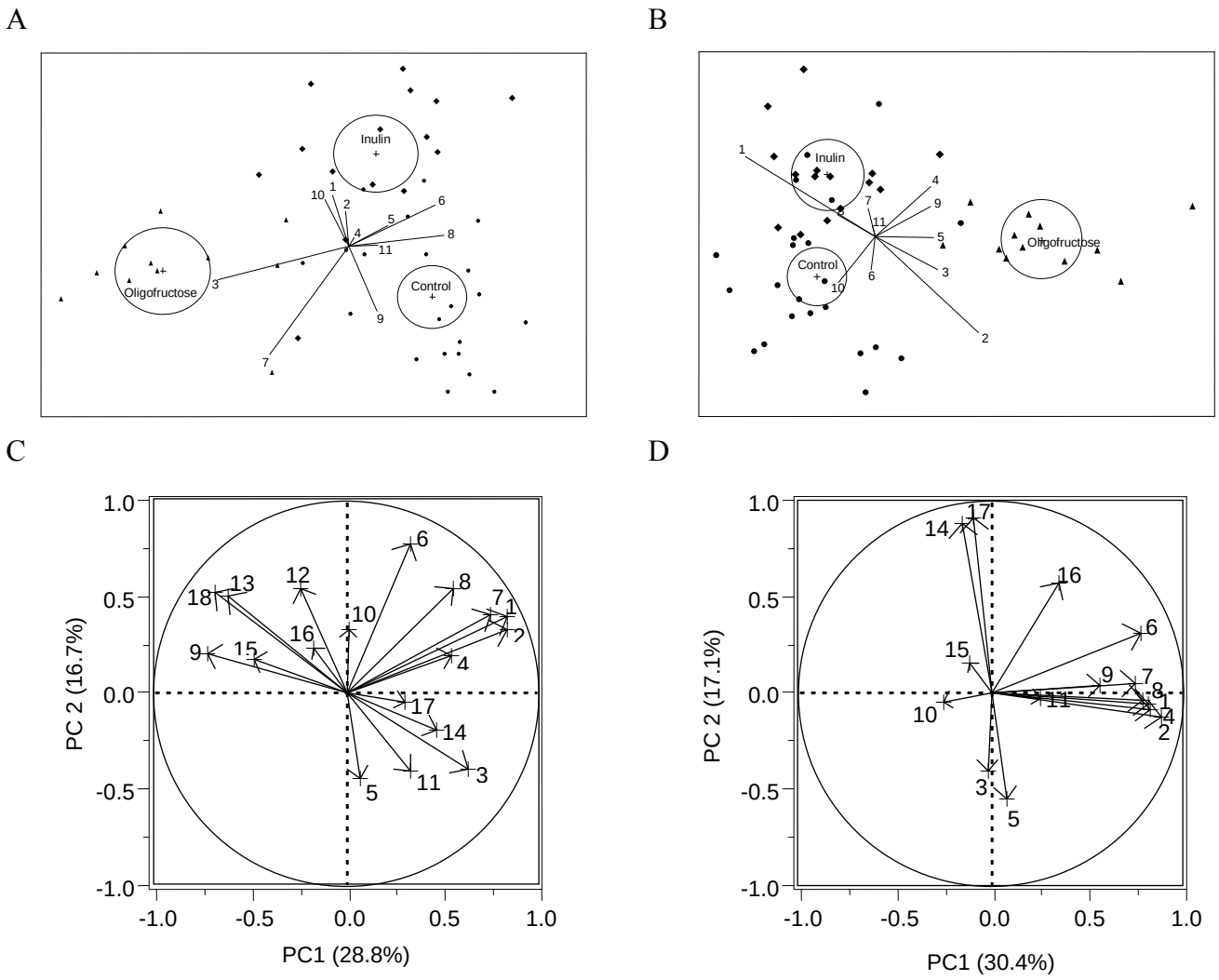

Figure 2. Linear discriminant analysis for cecum (A) and feces (B) of the control (●), inulin (◆) and oligofructose (▲) groups based on gene copies for bacterial group. Loading plots of the first two principle components (PC1 and PC2) for cecum (C) and feces (D) showing correlations among copy numbers for bacterial groups, short-chain fatty acids (SCFA), Gross Gut Score (GGS) and IL1-β concentration. 1 – total bacteria; 2 – *Bacteroides-Prevotella-Porphyromonas* group; 3 – *Bifidobacterium* ssp.; 4 – *Lactobacillus* ssp.; 5 – *Enterobacteriaceae* family; 6 – *Clostridium* cluster IV; 7 – *Clostridium* cluster XIVa; 8 – *Clostridium* cluster I; 9 – *Clostridium* cluster XI; 10 – *Clostridium difficile* toxin B; 11 – *Clostridium perfringens* alpha toxin; 12 – IL1-β concentration; 13 – GGS; 14 – acetate; 15 – propionate; 16 – butyrate; 17 – total SCFA; 18 – histology score.

Pioglitazone reduces angiogenesis by altering mitochondrial function and reducing HIF-1 activation

Dromparis P, Sutendra G, Bowers L, Haromy A, Hashimoto K, Stenson TH, Proctor S, Michelakis ED, and McMurtry MS.

Introduction: Thiazolidinediones (TZDs) used in type II diabetes are linked with adverse cardiovascular events by an unknown mechanism. TZDs can affect mitochondria, which are oxygen sensors and therefore can regulate the angiogenic transcription factor hypoxia inducible factor 1 (HIF1) via mitochondrial derived α-ketoglutarate (αKG) and reactive oxygen species (mROS). We hypothesized that pioglitazone (PIO), a TZD, may impair angiogenesis through a mitochondrial-HIF1-dependent mechanism.
Methods/Results: Human skeletal myocytes (hSMC) cultured at a pO_2 of 120 or 40mmHg were treated with PIO (20 μg/ml) for 24h. Compared to vehicle, PIO depolarized mitochondria and increased mROS and αKG in hypoxic hSMCs. PIO also decreased HIF1 activity (nuclear translocation and decreased VEGF, a HIF1 regulated gene). In vitro, using a matrigel assay, PIO directly inhibited human microvascular endothelial cell (hMVEC) angiogenesis (tubule formation). To assess the paracrine effects and exclude the direct PIO effects on hMVEC, we used a Boyden chamber matrigel bioassay where hSMCs and hMVEC were separated by a cell impermeable membrane. Pre-treatment of hypoxic hSMCs with PIO produced less angiogenesis than vehicle. In vivo, neovascularization was assessed in diabetic (JCR:LP; n=20) and non-diabetic (SD; n= 22) rats. Hindlimb ischemia was induced, and the rats were treated with a clinically relevant PIO dose (10mg/kg/day) or placebo for 14 days. Ischemic hindlimb (gastrocnemius) perfusion was decreased in PIO treated animals (contrast enhanced ultrasound and Tc^{99m} sestamibi micro CT-SPECT), which correlated with decreased angiogenesis (von Willebrand factor and lectin) in both diabetic and non-diabetic models.
Conclusions: PIO alters mitochondrial function in hSMC, reducing HIF1 activation and inhibiting both paracrine/autocrine angiogenesis. PIO also impaired angiogenesis in diabetic and non-diabetic rats. Impairment of angiogenesis is undesirable in human diabetics with concomitant atherosclerotic vascular disease, and may contribute to the recently recognized cardiovascular adverse effects of TZDs.

HIV-1 Nef Expression in the brain causes neuropsychiatric dysfunction

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Introduction: HIV-associated neurocognitive disorder (HAND) is defined by neuropsychiatric, neurocognitive and motor disfunctions, affecting 20% of AIDS patients. Because the HIV-1-encoded non-structural protein, Nef, is critical in HIV-1 infection, we examined Nef's actions in a novel transgenic model.

Methods: We generated Nef transgenic (Tg) mice (FVB) expressing Nef under the control of *c-fms* promoter permitting Nef expression in monocytoid cells. Transcripts and proteins were measured using sqRT-PCR and immunohistochemistry. Biogenic amines were determined by HPLC. Monoamine oxidase (MAO) enzyme activity was measured by radioactive assay. Neurobehavioral performance was assessed by locomotory, forced swim, elevated plus maze (EPM) and T-maze tests.

Results: Nef-Tg animals expressed Nef transcript and protein in the brain, particularly in the striatum and hypothalamus. Nef-Tg animals showed increased host immune gene expression including *CXCL12* and *MCP-1* in the hypothalamus, compared with littermate wildtype animals. Dopamine and serotonin levels were reduced in the hypothalamus but upregulated in the striatum of Nef-Tg animals ($p<0.05$), accompanied by decreased striatal MAO enzyme activity ($p<0.05$). Nef-Tg animals displayed augmented locomotor activity, decreased immobility in FST and increased open-arm exploration in EPM ($p<0.05$), all indicative of agitated/manic phenotype.

Conclusions: Nef expression in the brain caused a specific neurobehavioral phenotype, similar to what is observed in patients with HAND. This phenotype accompanied altered neurotransmitter and host immune transcript levels, also recapitulating aspects of HAND. Our findings point to a specific role for Nef in HAND pathobiology, making it an attractive target for preventative or therapeutic interventions.

Supervisor: Dr. Christopher Power

Dietary β-fructans is beneficial in mild to moderate ulcerative colitis and mediates specific luminal and mucosa-associated microbiota changes assessed by 16S rRNA pyrosequencing

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INTRODUCTION: The pathogenesis of inflammatory bowel disease (IBD) is attributed to an interaction of immune and environmental factors in genetically susceptible patients, also associated with intestinal dysbiosis. Non-digestible, fermentable carbohydrates (prebiotics) are able to stimulate the growth/activity of specific protective microbiota. Previously we showed that a mixture of inulin and fructo-oligosaccharides (FOS) reduced chronic colitis in HLA-B27 transgenic rats. The present study aimed to evaluate the effect of FOS and inulin in a small prospective open clinical trial with patients with active mild to moderate ulcerative colitis (UC) treated with oral 5-ASA. Specific microbiota changes induced by prebiotics were analyzed by qPCR and pyrosequencing of 16S rRNA genes to reveal the correlation between disease activity and biodiversity of mucosa-associated and luminal microbiota.

METHODS: Patients with mild to moderate active UC, on stable doses of oral 5-ASA were randomized to 7.5g or 15g daily oral inulin plus FOS (1:1) for 9 weeks. At weeks 0 and 9 patients were assessed for clinical disease activity and endoscopic activity; stool and biopsies were collected for fecal calprotectin and microbiota analysis. The microflora in fecal and biopsy samples was analyzed by pyrosequencing of 16S rRNA tags employing Titanium platform. Statistical analysis was performed by the Mann-Whitney test to identify differences in the fecal and biopsy microbiota composition.

RESULTS: Twenty four patients completed the trial and 6 patients withdrew. Fifty percent of the patients who completed the treatment showed a clinical response (12/24) of which 42% went into remission. Patients on 15g dose had an average decrease in UCDAI of 2.5 versus 1.2 in the 7.5 g dose. Clinical response was associated with a tenfold decrease of fecal calprotectin. The pyrosequencing analysis of 16S rDNA tags revealed that consumption of FOS and inulin increased the ratio of *Firmicutes* to *Bacteroidetes*; particularly pronounced in mucosal microbiota. Clinical response was associated with an increase of the bacterial diversity assessed by Shannon's and Simpson's diversity indices, with increased numbers of *Clostridium* cluster XIVa, and increased expression of the mucosal butyrate transporter.

CONCLUSIONS: Inulin and FOS reduced chronic inflammation and induced specific changes in luminal and mucosa-associated microbiota in patients with active UC who flared on oral 5-ASA. This small open label study indicates that these prebiotics show promise as adjunctive therapy to induce remission in mild to moderate UC.

SUPERVISORS: L. Dieleman, M. Gänzle

Title: Perfusion imaging predicts outcome in TIA and minor stroke

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Introduction: Clinical progression occurs in many patients presenting initially with minor or transient ischemic symptoms. Identification of the patients at highest risk for progression may justify more aggressive acute treatment prior to deterioration. We tested the hypothesis that baseline perfusion (PWI)-diffusion weighted imaging (DWI) abnormalities predict infarct growth and clinical progression.

Methods: Patients with minor stroke (NIH Stroke Scale ≤ 3) and TIA presenting within 12 hours of symptom onset were prospectively enrolled and imaged. DWI and PWI (within 24 hours of symptom onset) and follow-up FLAIR (30 days) infarct volumes were measured with planimetric techniques. PWI-DWI mismatch volumes were calculated as Tmax+4s delay – DWI lesion. Infarct growth volume was measured as day30 FLAIR -DWI lesion.

Results: 137 patients were included; 54% had DWI lesions and 41.6% had PWI (Tmax+4s) deficits at baseline. Clinical deterioration occurred in 13 (9.5%) patients within 72 hours. 119 patients had follow-up imaging at day 30, 21 of whom developed infarct growth (17.6%). Patients with clinical worsening had significantly higher baseline mismatch volumes (median= 45 ml, IQR= 83.3) than those who did not progress (median=0 ml, IQR= 1, P<0.001). A mismatch volume of 10ml predicted clinical worsening with 77% sensitivity and 86% specificity (Area Under Curve (AUC)= 0.814, [0.66, 0.9]) and radiographic infarct growth with 81% sensitivity and 91.5% specificity (AUC=0.883, [0.78, 0.98]). Linear regression showed that for every 10ml of mismatch, there would be 2.5ml infarct growth on day 30 FLAIR [R=0.80, p<0.001].

Conclusions: In a population of patients with minor stroke and TIA, early MR perfusion-diffusion mismatch strongly predicts clinical deterioration and infarct growth. These findings suggest that there may be a group of patients with minor symptoms in whom reperfusion strategies may be beneficial.

Human endogenous retrovirus-K envelope expression in neurons is protective in neuroAIDS

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INTRODUCTION: Human endogenous retroviruses (HERVs) represent 8% of the human genome and are expressed depending on the cell type and physiological circumstances. HERV-K has been implicated in the pathogenesis of several diseases including increased expression in blood from patients with HIV/AIDS. Herein, we investigated HERV-K envelope (*env)* expression and its actions in neuroAIDS.

METHODS: HERV-K *env* expression was assessed in neural cell cultures and brain tissues from HIV-infected and uninfected persons together with deep sequencing of healthy human brain tissues. The HERV-K *env* was cloned and expressed in different neural and non-neuronal cells with subsequent analyses of host responses as well as cellular viability.

RESULTS: Deep sequencing of human brain transcriptomes disclosed that HERV-K was the most abundant HERV detected in human brains, particularly fetal brains, which was correlated with host protein co-factor orthologous genes. Comparison of different cell types disclosed that HERV-K *env* transcript abundance was highest in cultured human fetal neurons but was suppressed by epidermal growth factor exposure. HERV-K *env* transcript and protein levels were increased in the cerebral cortex from persons with HIV/AIDS, observed chiefly in neurons ($p<0.05$). Human neuronal cells (SK-N-SH) transfected with HERV-K *env* exhibited increased nerve growth factor and brain-derived neurotrophic factor ($p<0.05$). In concert, HERV-K *env* over-expression in SK-N-SH cells increased cellular viability ($p<0.05$) and prevented neurotoxicity caused by cleaved the HIV-1 proteins, Tat and Vpr ($p<0.05$).

CONCLUSIONS: *In vivo* HERV-K expression was abundant in the human neurons, especially during HIV/AIDS. HERV-K *env* induction in neurons exerted a host protective response, which might underlie HERV-K's conservation within the human genome over the past million years.

SUPERVISOR(S): Power, C

Residence location, quality of care and adverse outcomes in diabetic subjects with CKD

Aminu Bello, Brenda Hemmelgarn, Meng Li, Braden J Manns, Bharati Ayyalasomayajula, Scott Klarenbach, Marcello Tonelli.
For Alberta Kidney Disease Network

Introduction: Rural and remote residence is a potentially reversible geographic barrier to care. We used a large cohort of people with diabetes and CKD in Alberta to investigate the relation between residence location, prevalent distribution of CKD, markers of good quality care, and the risk of clinically relevant adverse outcomes.

Methodology: From a cohort of 1,278,375 adult outpatients who had serum creatinine measured at least once during 2005 or 2006, we selected those with diabetes and eGFR 15-59 mL/min/1.73m^2. Subjects were classified into categories based on the distance by road between each individual's residence location and the location of the closest nephrologist (0-50, 50.1-100, 100.1-200, >200km). All-cause mortality and dates of hospitalization were determined by linkage to the provincial health records. Logistic and Cox regression analyses were done to examine the association between study outcomes and distance from the closest nephrologist.

Results: Of 31,337 eligible participants, 7,021(22.4%) lived >50 km from the nearest nephrologist. Over a median follow-up of 27 months, compared with those living within 50 km, those living further away were significantly less likely to visit a nephrologist or a multidisciplinary CKD clinic within 18 months of the index eGFR ($p<0.0001$). Similarly, remote-dwellers were less likely to have haemoglobin A1c measured within 1 year of the index eGFR measurement, less likely to have urinary albumin assessed biannually, and less likely to receive an ACEI, ARB or statin (all $p<0.0001$). In adjusted models, compared to subjects with CKD (stage 3 or 4) living within 50 km, the adjusted likelihood of all-cause hospitalization was (1.4 [95% CI, 1.3-1.6]), (1.3 [95% CI, 1.1-1.6]) and 1.3 [95% CI, 1.2-1.5]) fold higher for patients living 50.1-100, 100.1-200, and >200 km away from Nephrologist respectively, (all $p<0.0001$). The hazard ratio of all-cause mortality also increased with increasing distance: 1.07 [95% CI, 0.9-1.2]), 1.1 [95% CI, 0.9-1.2]) and 1.2 [95% CI, 1.0-1.4]) respectively, (all $p<0.0001$).

Conclusions: Even in a universal healthcare system as obtained in Canada, remote-dwellers with diabetes and CKD were less likely to receive specialist care, recommended laboratory testing and appropriate medications as compared to those living closer to a nephrologist, and were more likely to experience adverse outcomes for all-cause hospitalization and mortality. Future studies of new technologies such as telehealth should evaluate how to improve care in this disadvantaged category of the population.

Use of population-based conventional and molecular data in pediatric tuberculosis (TB) to understand TB transmission in Canada

Dhawan V, Lau A, Kunimoto D, Bhargava R, Long R

INTRODUCTION: Study of TB transmission is critical to the success of any TB elimination program. Pediatric TB is a marker of recent and ongoing TB transmission in a population. An understanding of pediatric TB and its epidemiology can help inform TB elimination strategy.
METHODS: All pediatric TB cases over a period of 20 years (1990-2009) were identified in the Alberta TB registry. Individual diagnostic criteria were reviewed and case patients were related to different population grids. Incidence rates were determined by population group and gender. Microbiological and DNA fingerprinting data on the *Mycobacterium Tuberculosis* isolates were obtained from the Provincial Laboratory for Public Health. Two or more isolates with identical DNA fingerprints were grouped as clusters and the rest as non-clustered isolated cases. Clinical-demographic data of these two groups were compared.
Results: After applying strict pediatric TB case definition, 144 pediatric cases were identified: 53 Status Indian (SI), 49 Canadian born other (CBO) and 42 foreign-born (FB). Crude incidence rates (per 100,000 person-year) were 9.16 (SI), 0.44 (CBO) and 6.95 (FB) respectively. 54 cases (37.5%) were culture-positive and out of which 37 were clustered and 16 were non-clustered isolate cases. 51% of the clustered cases were among SI and a majority of them were females. 75% of the non-clustered isolate cases were among FB.
Conclusion: A high degree of clustering among SI children suggested that transmission was ongoing within this community. A majority of non-clustered isolated cases were among FB suggesting that TB was acquired outside Canada and TB screening of recently arrived children from high incidence countries for latent TB infection should be expanded. Focusing screening measures among these high-risk population groups can help improve TB control program.

Supervisor: Dr. Richard Long

Cardiac MRI For Patients with Ventricular Arrhythmias but Normal Hearts by Conventional Testing

Dr. Mikael Hanninen, Dr. Nakul Sharma, Dr. Ian Paterson

Background: No structural heart disease is identified by conventional methods in 5% of patients with ventricular tachycardia (VT) and sudden cardiac death (SCD). Cardiac MRI (CMRI) late gadolinium enhancement (LGE) has shown promise in predicting VT in hypertrophic and dilated cardiomyopathy, but the utility of CMRI among patients without heart disease by conventional testing remains unknown.
Hypothesis: In patients with VT, but no heart disease during routine workup, CMRI will show LGE and help predict adverse arrhythmic events.
Methods: All consecutive patients undergoing CMRI for VT or SCD at the Mazankowski Alberta Heart Institute from 2006-2010 were screened and conventional testing (electrocardiogram, coronary angiogram, echocardiogram) reviewed to exclude patients with heart disease. CMRI LGE was correlated with inducible VT during EP testing and appropriate ICD shocks using regression analysis.
Results: 140 patients had CMRI for VT and 69 were free from heart disease by conventional testing. Of the 27 patients who had EP testing, 40% had inducible VT. 6 patients received an ICD (4 for SCD and 2 for syncope). CMRI LGE did not correlate with inducible VT (p=0.74) or appropriate ICD shocks (p=0.21). 4 patients without heart disease by routine workup had epicardial LGE, but only one also had inducible VT at EP testing – this patient's LGE site and VT focus coincided and ablation terminated the VT. No VT-related hospitalization or death was seen in the other patients with CMRI LGE.
Conclusions: The yield of CMRI in patients without heart disease by usual testing is low. CMRI LGE did not always correlate to inducible VT at EP study or adverse arrhythmic events at follow-up. Therefore, we do not feel that CMRI should be routinely performed in patients with VT, but no heart disease by conventional testing.

Baseline Characteristics, CMRI Findings and Clinical Outcomes (n=69)

Demographics	Mean / %
Age at time of CMRI (yrs)	39
Male (%)	55%
Followup (mo)	36
SCD or Syncope with VT	9%
CMRI findings	**# (%)**
Late gad enhancement (epicardial)	4 (6%)

Clinical Outcomes	# (%)
EPS	27 (39%)
- Inducible VT	11 (41%)
*RVOT VT	6
*Fascicular VT	2
*CPVT	2
*Epicardial VT	1
ICD implantation	6 (9%)
- Appropriate ICD shocks	4 (67%)

Evaluating Cardiac Risk in Systemic Lupus Erythematosus versus Other Inflammatory Arthritis Patients

Teo M, Hartmann D and Keeling S.

Objective: Systemic Lupus Erythematosus (SLE) and other inflammatory arthritides (OIA) are independent risk factors for cardiovascular disease (CVD). Cardiovascular risk stratification scoring systems are a starting point in evaluating CVD risk. The main study objective was to determine how effective rheumatologists are at CVD risk stratification in SLE patients and compare this to OIA patients.

Methods: A retrospective chart review of 504 patients attending the practices of nine rheumatologists at the University of Alberta Hospital was performed with pre-specified case report forms reviewing disease indices and medications, cardiac risk factors and Framingham 2008 and Reynolds risk scores.

Results: In this group of 504 patients, 64 (12.7%) had SLE (M:F =4:60), 440 (87.3%) had an OIA (M:F =117:323). Of the SLE patients, 33 (51.6%) met four or more ACR criteria, 31 (48.4%) had less than four ACR criteria. Of the OIA patients, 156 (35.5%) were CCP positive and 257 (58.4%) were RF positive. Complete Framingham risk scores were calculable for 1 (1.6%) SLE patient and 3 (0.68%) OIA patients. The Reynold's risk score was not calculable for any patients. The number (%) of SLE vs. OIA patients where common cardiac risk variables were not recorded included: (1) positive family history of MI 62 (96.9%) SLE vs. 440 (100%) OIA patients, (2) diabetes 62 (96.9%) SLE vs. 421 (95.7%) OIA patients, (3) lipids status 48 (75%) SLE vs. 322 (73.2%) OIA patients and (4) smoking status 35 (54.7%) SLE vs. 275 (62.5%) OIA patients. The number (%) of SLE vs. OIA patients where cardiovascular medications (whether positive or negative) were recorded included: ASA 62 (96.9%) SLE vs. 311 (70.7%) OIA patients, anti-hypertensives 62 (96.9%) SLE vs. 317 (72.0%) OIA patients, and lipid lowering medications 61 (95.3%) SLE vs. 310 (70.5%) OIA patients. Systolic blood pressure was documented in 60 (93.8%) SLE and 247 (56.1%) OIA patients

Conclusions: Cardiovascular risk assessment in both SLE and OIA is sub-optimally performed by rheumatologists. Cardiovascular medication history and blood pressure documentation in SLE patients, however, is better than that of the OIA's. The multi-system nature of SLE including renal disease potentially leads to closer monitoring of CVD risk factors such as diabetes and hypertension. Increased documentation of CVD risk factors and possible use of existing risk scores is the first step in establishing effective CVD risk reduction in these higher risk rheumatic disease groups.

THE EFFECT OF CLOSTRIDIUM DIFFICILE INFECTION ON OUTCOME IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE.

V. Selvarajah and R. N. Fedorak, University of Alberta.

Background: Clostridium difficile associated disease (CDAD) has been increasing in incidence across Canada and can result in significant morbidity and mortality. Patients with inflammatory bowel disease (IBD) are known to have an increased frequency of CDAD. The aim of this study was to characterize IBD patients who develop CDAD and evaluate their clinical outcome when compared to IBD patients without CDAD.

Methods: We identified, using ICD-9 codes, patients discharged from the University of Alberta Hospital between 2000 to 2010, who were admitted with an acute flare of IBD and also had a confirmed diagnosis of CDAD during the hospital stay. This was compared to a randomly selected group of IBD patients admitted with a flare of IBD, without evidence of CDAD. Demographic information in addition to colectomy, mortality, CDAD relapse and IBD flare rates were obtained over 12 months for both groups.

Results:

Table 1. Patient Profile

	N, CDAD(%)	N, controls(%)
Total Admissions	45	42
Distinct Patients	39	42
Age(mean)	45.76+-20.2	32.16+-15.8
Sex, Male	16	27
Crohns Disease	17(44%)	23(55%)
Ulcerative Colitis	22(56%)	19(45%)
Recent Abx	28(62%)	11(26%)
Corticosteroids	22(49%)	20(48%)
5-ASA	24(53%)	17(40%)
Azathioprine	8(18%)	10(24%)
Methotrexate	1(2.2%)	1(2.3%)
Biologics	0	9(21%)
Proton Pump Inhibitor	11(24%)	8(19%)
Recent Hospitalization	21(47%)	2(5%)
Prev C difficile	13(29%)	0

Table 2: Outcomes

	CDAD(%)	Control(%)
Mortality		
Within 3 months	4(8.9%)	0
3 - 6 months	1(2.2%)	0
Total within 12 months	5/45(11.1%)	0/42
Colectomy		
Within 3 months	3(6.7%)	1/42(2.4%)
3-6 months	1(2.2%)	0
Total within 12 months	8(17.8%)	1(2.4%)
		OR 8.9
Total Major Events	13/45(29%)	1/42(2.4%)
		OR 16.7
Recurrence (<12months)	14/45(31.1%)	0
IBD Flare (<12months)	21/45(46.7%)	12/42(28.6%)
		OR 2.2
LOS(mean, days)	17.02+-25.2	9.67+-8.0

Conclusion:

IBD patients admitted to hospital with CDAD have higher rates of IBD flare, increased length of hospital stay and increased colectomy and death rates compared to IBD patients without CDAD. Recent hospitalization, antibiotic use, previous CDAD and age were associated with CDAD development in patients with IBD. Empiric antibiotic use, concurrent use of corticosteroids, dual therapy with vancomycin and metronidazole and age are factors associated with increased rates of colectomy and/or death in IBD patients with CDAD.

COMPARISON OF TRIPLE THERAPY, QUADRUPLE THERAPY AND SEQUENTIAL THERAPY FOR THE ERADICATION OF *HELICOBACTER PYLORI* INFECTION

Pinchbeck, M. and Veldhuyzen van Zanten, S. Division of Gastroenterology.

INTRODUCTION: *Helicobacter pylori* infection can cause ulcer disease, MALT lymphoma and gastric cancer. The current recommended first line *H. pylori* treatment consists of a proton pump inhibitor, clarithromycin and amoxicillin (PPI-CA) or metronidazole (PPI-CM). However, triple therapy eradicates *H. pylori* in less than 80% of cases. Alternative treatments include quadruple therapy with bismuth, tetracycline, metronidazole and PPI, and sequential therapy with PPI and amoxicillin for 5 days, followed by PPI-CM for the next 5 days. The objective of this study was to determine the efficacy of these regimens for the eradication of *H. pylori* in the Edmonton area.

METHODS: Patients diagnosed with *H. pylori* infection on histology or urea breath test were eligible for this retrospective cohort study. Patients who did not comply with therapy or have post-treatment testing for *H. pylori* eradication were excluded. Data was collected on treatment regimens used and eradication testing. The efficacy of triple, quadruple and sequential therapy was calculated.

RESULTS: 141 patients were eligible for study inclusion. 60 (43%) were male, and the mean age was 52.5 ± 13.8 years. 8 patients (5.7%) did not comply with treatment and were excluded. Of the 133 patients who received treatment, 92 (69.2%), 13 (9.8%), and 24 (18.0%) received PPI-CA, PPI-CM, and sequential therapy as first-line, respectively. Second, third, and fourth courses of therapy were required in 42/133 (31.6%), 13/133 (9.8%), and 3/133 (2.3%) patients, respectively. 32/33 (97.0%) patients received quadruple therapy for failure of other treatment. Post-treatment eradication testing followed 163/191 (85.3%) courses of therapy. *H. pylori* was eradicated in 45/82 (54.9%) PPI-CA, 4/14 (28.6%) PPI-CM, 23/29 (79.3%) quadruple therapy, and 18/20 (90.0%) sequential therapy cases.

CONCLUSIONS: The efficacy of standard triple therapy for *H. pylori* is unacceptably low and worse than previously reported. Sequential therapy was superior to triple therapy for first-line treatment. Quadruple therapy was the most effective second-line therapy.

SUPERVISOR: Dr. S. Veldhuyzen van Zanten

Renal Outcomes Following Emergent Repair of Ruptured Abdominal Aortic Aneurysms

Kopolovic I, Stollery DE, Ewanchuk M, Duggan S, Bagshaw SM

INTRODUCTION: Ruptured abdominal aortic aneurysm (AAA) is associated with considerable mortality and morbidity. The objective of this study was to describe the incidence of post-operative acute kidney injury (AKI), characterize its risk factors, course and associated clinical implications in ruptured AAA.

METHODS: Retrospective cohort study. All patients receiving emergent repair of ruptured AAA in the Edmonton Capital Zone from January 1, 2002 to December 31, 2009 were eligible. Data were captured on demographics, pre-existing co-morbidities, intra-operative and post-operative course, and clinical outcomes. AKI was defined by the Acute Kidney Injury Network (AKIN/RIFLE) criteria.

RESULTS: During the study, 141 patients presented for emergent repair of ruptured AAA. Mean (SD) age was 71.2 (8.3) years, 85.8% were male, 70.2% had pre-morbid hypertension, 36.0% had coronary artery disease, and 19.2% had chronic kidney disease. Open repair was the predominant procedure performed (96.4%). Of 141 patients, 68.1% developed post-operative AKI, and 13.3% required renal replacement therapy (RRT). AKI severity, stratified by maximum post-operative AKIN/RIFLE category, were RISK in 22.7%, INJURY in 23.5%, and FAILURE in 15.5%. Post-operative AKI was associated with prior CKD (25.0% vs. 6.7%, odds ratio [OR] 3.8 (95% CI, 1.2-11.8), p=0.007), higher APACHE II score (25.6 (7.6) vs. 18.3 (7.8), p<0.001), and post-operative positive cardiac-specific troponin (65.3% vs. 33.3%, OR 2.0 (95% CI, 1.2-3.1), p<0.001). Mortality in ICU (28.1% vs. 6.8%, OR 5.3 (95% CI, 1.6-17.5), p=0.003), in hospital (35.4% vs. 6.8%, OR 7.5 (95% CI, 2.3-24.4), p<0.001) and at 1-year (41.5% vs. 19.0%, OR 3.0 (95% CI, 1.3-7.1), p=0.008) were significantly higher for those with AKI. Mortality increased linearly with increasing AKI severity (p<0.001) and was highest in those requiring RRT.

CONCLUSIONS: Acute kidney injury following ruptured AAA is common and portends worse outcomes. Those with pre-existing CKD, higher illness severity, and biochemical evidence of myocardial injury are at elevated risk for post-operative AKI.

IMPACT OF DEDICATED CANCER CENTRE SURVEILLANCE ON GUIDELINE ADHERENCE AND OUTCOMES FOR STAGE II AND III COLORECTAL CANCER (CRC) PATIENTS (pts)

Standeven L, Mulder K, Spratlin J, and Price Hiller J

INTRODUCTION: In response to low adherence rates to CRC surveillance guidelines in pts undergoing community-based follow up (<10% adherence in our previous study), an innovative surveillance program was established at our center. We evaluated adherence to surveillance recommendations and outcomes of this program.

METHODS: A retrospective chart review was conducted on stage II/III CRC pts who completed curative intent treatment from 2007-2009. Surveillance recommendations included: 1) carcinoembryonic antigen (CEA) blood test every 3 months for 3 years, 2) computed tomography (CT) scan of chest/abdomen/pelvis at 1 and 2 years post-surgery, and 3) colonoscopy within 1 year of surgery.

RESULTS: To date, 207 of 461 pts have been evaluated (median age 68, 62% male, 69% colon, 59% stage III). Median duration of surveillance was 1.6 years. Overall, 51% of pts were adherent to all components of surveillance. Non-adherence was due to lack of CEAs in 25%, CT scans in 11%, and colonoscopy in 31%. Reasons for non-adherence included patient non-compliance (23%), cancer centre scheduling (33%), and indeterminate/other (49%). 45% of pts had at least one abnormal surveillance investigation leading to 100 imaging investigations. 14% of pts were diagnosed with recurrent CRC. 83% of recurrences were diagnosed due to surveillance investigations and 30% of recurrences were considered potentially resectable. Respectively, 19% and 10% of adherent and non-adherent pts were diagnosed with a recurrence. Final results will be forthcoming.

CONCLUSIONS: Preliminary results suggest an improvement in adherence to CRC surveillance recommendations since the program began; however, adherence rates are still not optimal. Both patient and provider-related factors contributed to non-adherence. Alterations in management for monitoring these pts are suggested.

A Wise Investment? Modeling industry profitability and risk of targeted chemotherapy for incurable solid cancers

Conter, Henry; Ohinmaa, Arto; Chu, Quincy SC

Background:

Despite significant investment into targeted chemotherapy as treatment for incurable solid cancers, the majority of new protocols incorporating these treatments are unsuccessful in improving survival outcomes. We set out to derive an economic model to aid in decision-making for further private investment by clarifying acceptable levels of phase III clinical trial risk

Methods:

A literature search was performed to determine event probabilities, clinical trial costs, and total expenses as inputs into the model.

Results:

To avoid suffering losses, the average maximum allowable risk-adjusted expense per molecule brought to market should be $802 million USD in 2000 dollars. For anti-cancer agents, the expected capitalized cost per approved drug may rise to $1,042 million USD. Phase III clinical trials represent 37.4% of the clinical expenditure in drug development. Fixing the risk-adjusted allowable expense throughout the drug development process, the maximum acceptable phase III

trial failure rate becomes 61%. Currently, from inception to April 2010, the phase III failure rate is 57% with regards to progression free survival and 87% with regards to overall survival.

Conclusions:

Although the investment risk of proceeding with phase III clinical trials for targeted chemotherapy for incurable solid cancers seems high, the current level risk is acceptable. The "breakeven" total expense inputs included in this model incorporated an annualized return on investment of 11%. Pharmaceutical companies may be charging more for targeted treatment than their investment risk level would suggest.

Abstract

The unrecognized burden of osteoperosis-related vertebral fractures in patients with heart failure

Lyons KJ, Majumdar SR, Ezekowitz JA

Methods: We conducted a prospective cohort study in a random sample of patients attending a tertiary care HF Clinic in Edmonton, Alberta, Canada. We collected sociodemographic, clinical, medication, and chest-radiograph information. Primary outcome was board-certified radiologist documented VCF on chest radiographs. Multivariable logistic regression was used to determine independent correlates of VCF.

Results: Overall, 623 patients with HF were included; 32% were over 75 years of age, 31% were women, 65% had ischemic cardiomyopathy, and 38% had atrial fibrillation. Prevalence of VCF was 77 of 623 (12%; 95%CI 10 to 15%) and 42 of 77 (55%) patients had multiple fractures. Only 15% of those with VCF were treated for osteoporosis. In multivariable analyses adjusted for age, female sex, weight, and medications, the only remaining predictors independently associated with fracture were atrial fibrillation (present in 42 of 77 [55%] of those with VCF vs. 197 of 540 [36%] of those without; adjusted odds ratio 2.1, 95%CI 1.2 to 3.6, p=0.009) and lipid lowering drugs (used by 36 of 77 [47%] of those with VCF vs 342 of 540 [63%] of those without; adjusted odds ratio 0.2, 95%CI 0.1-0.9, p=0.03).

Conclusions: About one-tenth of HF patients had a chest-radiograph documented VCF and half of those with VCF had multiple fractures; most (85%) were not on an osteoporosis-specific therapy. A previously unrecognized risk factor – atrial fibrillation – was found to be independently associated with VCF. Chest radiograph reports may represent an important case-finding tool for osteoporosis-specific VCF, particularly in HF patients with atrial fibrillation.

Utility of a schematic assessment tool to aid in the evaluation of internal medicine residents' clinical diagnostic reasoning skills: a pilot study

Jason Kiser, MD and Bruce Fisher, MD

Abstract

INTRODUCTION
A key component to clinical competence in medical practice is the ability to problem solve. There is a paucity of evidence as to its measurement in learners at all levels of training. This pilot study attempts to determine the utility of a schematic assessment tool in providing consistent and reliable feedback to internal medicine residents after observed diagnostic reasoning performances.

METHODS
12 third-year internal medicine residents were randomly assigned to control and experimental groups. Each of the groups participated in separate 45-minute workshops where the principles of feedback and diagnostic reasoning skills were demonstrated. Participants in the experimental arm also received training in the application of a schematic assessment tool designed to aid in observing and analyzing the various component parts of diagnostic reasoning. Following the introductory session, each group separately participated in three, one hour videotaped sessions where a facilitator provided a resident a common, undifferentiated clinical scenario and asked the resident to work through the case while undertaking a "thinking out loud" approach. The remaining participants independently recorded their assessment and feedback on standardized questionnaires comprised of a Likert scale and two questions used to elicit written observations and feedback. Upon completion of the live sessions, the videotaped sessions were displayed to the other group until both groups had evaluated all sessions. Likert scores were compiled to measure the degree of agreement between observers, and narrative feedback was analyzed for potential differences between the two groups.

RESULTS
The analysis of Likert scores for the same observed diagnostic reasoning performances failed to demonstrate any statistically significant differences in scores assigned by the two groups. Also, there were no significant intra-group differences between scores assigned to the same observed performances. However, narrative analysis of the written observations and feedback suggest that the two groups may have paid attention to different components of performance.

CONCLUSION
These results suggest that the intervention may have influenced the experimental group's approach to observing diagnostic reasoning but may have been insufficient to enable better evaluation of diagnostic reasoning performance and intra-observer agreement. Whether more training in the use of schematic assessment tools would accomplish this goal will be the subject of further investigations.

SUPERVISOR
Bruce Fisher, MD

Diagnosis of Aortoenteric Fistulas Not to be Missed: Case Report of Unusual Duration of Bleeding

Lu, C, Wiebe, E, Semlacher, E.

INTRODUCTION

Vaso-enteric fistula, commonly also referred to as aortoenteric fistula (AEF) is a pathologic direct communication between a major artery (usually aorta) and the gastrointestinal (GI) tract. When left untreated, an AEF invariably results in death of the patient. AEF's occur almost exclusively in the setting of vascular graft replacement and only rarely occurs from a connection with a native blood vessel. Therefore, the diagnosis must be seriously considered whenever overt GI bleeding occurs in patients with vascular grafts in the chest or abdomen. Many AEF bleeds will have initial self-limited "herald" bleeding before an exsanguinating bleed occurs. The evaluation of such an event must be urgent as the next bleed may be fatal. However, the diagnosis can be wrongly excluded when multiple bleeding episodes have occurred over weeks to months. If intermittent bleeding occurs over such a period, the possibility of AEF is generally not considered. We present a rare case of an AEF with recurrent bleeds over a period of 8 months.

CASE PRESENTATION

Mr. EP, a 79 year old man, with an aortic graft placed 6 years earlier presented with 3 episodes of acute GI bleeding with melena and a sizable decrease in his hemoglobin over a period of 8 months. Initially, a CT scan and repeated upper endoscopies did not clearly identify the source of blood loss. The presence of an AEF was successfully confirmed after a second CT scan was later performed after a recurrent episode of melena and the possibility of AEF was strongly considered.

CONCLUSIONS

It is imperative to recognize AEF in the setting of GI bleeding as the condition is inevitably fatal. It should be suspected in all patients who have an abdominal aortic aneurysm or a prosthetic graft who present with extensive bleeding. However, we demonstrate that in patients with past vascular graft surgery, AEF is possible even with multiple bleeding episodes over many months which is contrary to popular belief. The diagnosis of AEF must not be negated in these circumstances.

SUPERVISOR

Dr. E Semlacher

Non-Invasive cardiac workup protocol for liver transplant candidates

Ye C, Saincher M, Tandon P, Burak K, Meeberg G, Bain VG

Ischemic cardiac events are major contributors to morbidity and mortality in patients post-liver transplantation. There is currently no validated protocol to screen for high-risk patients pre-transplantation and many patients were being referred for coronary angiography as part of their workup.
Objectives: (1) Introduce a non-invasive cardiac screening protocol; (2) determine if it decreases the number of coronary angiograms; and (3) compare post-transplant cardiac outcomes using the new protocol to an appropriately matched historical control group.
Methods: A new cardiac screening protocol [Figure 1] was introduced in 2005 at the University of Alberta Hospital for liver transplantation, which utilizes perfusion scintigraphy to screen high cardiac risk patients, reserving coronary angiograms for abnormal results. Patients screened by this protocol and transplanted by February 2009 were included in our study. These patients were matched to historical controls by age, gender, cardiac history and diabetes status. Electronic charts were reviewed for cardiac outcomes post-liver transplantation. Statistical analysis was performed using SPSS.
Results: 396 patients went through the cardiac screening protocol between April 2005-February 2009. 84 of the 396 patients were transplanted by February 2009; 2 patients were excluded from analysis due to concomitant kidney transplant. We successfully matched 81 patients. There were no significant differences in baseline characteristics between the two groups. 13/82 (15.9%) and 11/81 (13.6%) in the case and control groups, respectively, received coronary angiograms. Coronary artery disease (CAD) was found in 6/82 case patients, with none requiring percutaneous coronary intervention (PCI), and 5/81 control patients, including 2 patients with critical lesions requiring PCI. Transplanted patients were followed to study closure or death, with a mean follow-up of 1.87 years (+/- 0.91 SD) and 4.45 years (+/-1.89 SD) in the case and control groups, respectively. No intra-operative coronary events occurred in either group. 2/81 in the control group and 0/82 in the case group had an acute coronary syndrome event post-operatively.
Conclusion: Using this cardiac screening protocol did not reduce the number of coronary angiograms performed, but we can conclude that this primarily non-invasive cardiac workup protocol applied selectively according to cardiac risk factors is a safe and effective method of screening for CAD prior to liver transplant.

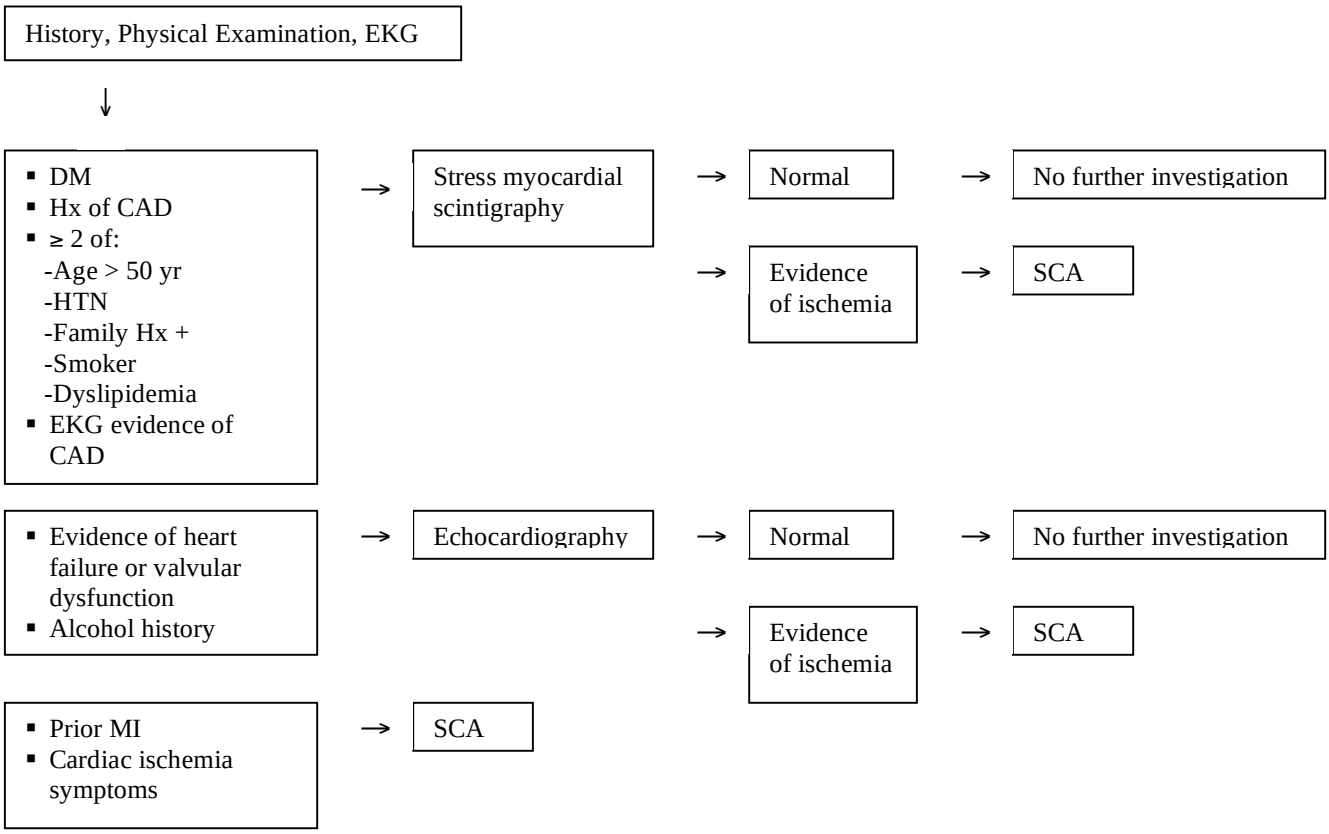

Figure 1: Cardiac workup protocol for liver transplant candidates. OLT=orthotopic liver transplantation, DM=diabetes mellitus, NCAD=non-cardiac atherosclerotic disease, HTN=hypertension, MI=myocardial infarction, SCA=selective coronary angiography.

FEATURES AND OUTCOMES OF PATIENTS WITH OVERLAP SYNDROMES AFTER LIVER TRANSPLANTATION

Rahima A. Bhanji, M.D. and Aldo J. Montano-Loza, M.D.

Background/Aims: The term overlap syndrome describes variant forms of autoimmune hepatitis (AIH) that present in combination with either characteristics of primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC). In end-stage liver disease due to overlap syndrome, orthotopic liver transplantation (OLT) is considered to be the treatment of choice. This study describes the characteristics of patients with overlap syndrome who have undergone OLT, as well as reports recurrence and long-term outcomes. *Methods:* Ten patients with overlap syndromes from a total of 1,040 patients who received liver transplants over the period of 1989 to 2010 were evaluated. Seven of these patients had AIH-PBC and three had AIH-PSC. Patient characteristics including gender, age, co-morbid diseases, biochemical, immunological profiles, and recurrence of disease were obtained. *Results:* Mean age at OLT was 41±18 years, and eighty percent were women. MELD score before OLT was 15±5 points, and Child-Pugh score was 8±1.2 points. The duration from overlap syndrome diagnosis to OLT was 59±34 months. Seven patients had recurrent disease within 35±30 months. Probability of recurrent disease was 73% at 5 years, and 86% at 10 years. Mean survival was 133±15 months (95% CI, 104-162) and the 5 and 10-years probability of survival after OLT was 88%. *Conclusions:* Our study showed that overlap syndromes are an infrequent indication for OLT; as in the past two decades, in our liver transplant program, less than 1% of transplants were done in this group of patients. In addition, we observed a higher rate of

disease recurrence; however, overall survival after OLT was good and comparable to that reported for single autoimmune liver diseases.

Intranasal Ipratropium Bromide for the Common Cold

Albalawi ZH, Othman SS and Alfaleh K

INTRODUCTION

Common cold is the most common illness in humans and constitutes an economic burden both on productivity and expenditure for treatment. There is no effective therapy for the common cold and symptomatic relief is the mainstay of treatment. The use of intranasal ipratropium bromide (IB) has been addressed in several trials, and might prove an effective treatment for rhinorrhea in the common cold.

METHODS

The search strategy included the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, AMED, Biosis and LILACS. We included randomised controlled trails (RCTs) comparing IB to placebo in children and adults with the common cold. Two review authors independently extracted data and assessed trial quality. Abstracted data included subjective change in rhinorrhea and nasal congestion, global assessment of overall improvement, and side effects. The protocol has been published in The Cochrane Database of Systematic Reviews.

RESULTS

Of the 342 results generated, seven trials with a total of 2,144 participants were included. Four studies (1,959 participants) addressed subjective change in severity of rhinorrhoea. All studies were consistent in reporting statistically significant changes in favor of IB. Nasal congestion was reported in four studies, and was found to have no significant change between the two groups. Two studies found a positive response in the IB group for the global assessment of overall improvement. Side effects were more frequent in the IB group, odds ratio (OR) 2.09 (95% confidence interval (CI) 1.40 to 3.11). Commonly encountered side effects included nasal dryness, blood tinged mucous and epistaxis.

CONCLUSION

For people with the common cold, IB is effective in ameliorating rhinorrhoea. Its use was associated with more side effects compared to placebo, although these appeared to be well tolerated and self-limited.

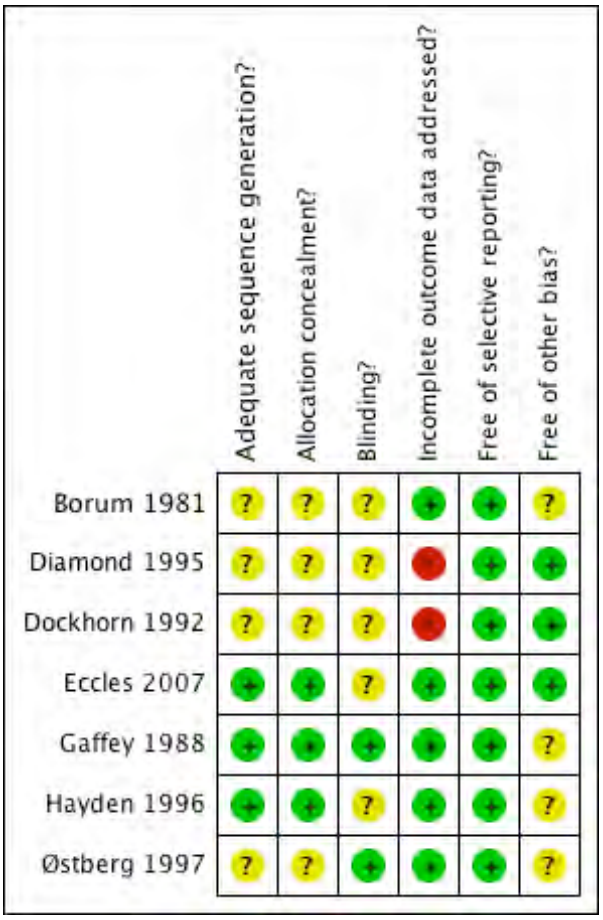

Figure1.Risk of bias summary

Dietary non-digestible carbohydrates modulate gut injury induced by CPT-11 based chemotherapy in rats with colon cancer

Farhangfar A, Meijer BJ, Lin X, Valcheva R, Baracos V, Field C, Gänzle M , Sawyer M, Dieleman LA

INTRODUCTION:The pathobiology of mucosal injury after CPT-11 chemotherapy, likely mediated by its metabolite SN-38 after conversion by bacterial β-glucuronidase, involves damaged intestinal barrier, intestinal microflora alterations and impaired intestinal and systemic immunity.The aim of our study is to assess the effect of various Non-digestible carbohydrates(NDCHOs) on this chemotherapy-induced gut injury.
METHODS:Rats bearing the Ward colon tumor were treated with 2 cycles of CPT-11/5FU.Animals were fed 7 different semi-synthetic diets including 10%(w/w) fibre as cellulose,inulin,Oligofructose(OligoF),a mixture of inulin and oligoF,isomalto-oligosaccharide(IsoM),type IV resistant starch(RS4) or 2% cellulose.Animals were killed 2 days after the 2nd chemotherapy cycle and were assessed for constitutional indices(weight, food intake), immune cell phenotypes in mesenteric lymph nodes(MLN), intestinal microbiota changes and their metabolic function.
RESULTS:Variations in dietary NDCHO fractions corresponded to significant variation in clinical and biological indices of toxicity, with the least toxicity in animals fed RS4 or inulin+oligoF and greatest toxicity in animals fed IsoM or 2%cellulose.IsoM or 2% cellulose diets were associated with significantly($p<0.05$)greater weight loss, lower food intake, lower levels of total T cells and cytotoxic T(CD8+)cells in MLN, higher levels of antigen presenting cells and expression of activation markers(CD28, CD71, CD152) on CD8+ cells, higher levels of *Enterobacteriaciae* and reduced butyrate levels in caecal digesta and lower plasma glutamine.Unexpectedly, a high cecal glucoronidase activity was associated with low toxicity of CPT-11 chemotherapy.
CONCLUSIONS: This is the first controlled comparison of multiple NDCHOs with putative and beneficial actions in chemotherapy-induced intestinal injury.Diets with RS4 or inulin+oligoF were particularly beneficial.These findings indicate that dietary NDCHO contents could modify chemotherapy-induced gut injury.
SUPERVISORS: Baracos V, Dieleman LA

Abstract Unavailable

Endoplasmic Reticulum Stress is Critical in the Pathogenesis of Pulmonary Arterial Hypertension and an Important Therapeutic Target

Dromparis P, Sutendra G, Paulin R, Haromy A, McMurtry MS, Vance JE, Michalak M, Sessa WC and Michelakis ED

INTRODUCTION: Pulmonary arterial hypertension (PAH) is associated with a number of diverse etiologies (BMPR2 mutations, hypoxia, viruses) that all result in a remarkably similar proliferative and apoptosis-resistant phenotype. Common among those is endoplasmic reticulum (ER) stress. Reticulon-4B (Rtn4B), which is induced by the ER stress-sensitive transcription factor ATF6, regulates ER shape and may function as a pro-survival factor.
Hypothesis: ER stress-induced Rtn4B is central in PAH pathogenesis and its inhibition reverses/prevents PAH.
RESULTS/METHODS: Rtn4B levels are elevated in the serum (n=41) and pulmonary arteries (PAs; n=5) of PAH patients compared to healthy (n=18) and secondary pulmonary hypertension patients (n=6) ($p<0.001$). The redox-sensitive ATF6 was activated in PAH and hypoxic PA smooth muscle cells (SMC), but not systemic arterial (carotid, renal) SMC, resulting in pulmonary-selective induction of Rtn4. Induced Rtn4 resulted in both a structural (electron microscopy) and functional (phospholipid bioassay) disruption of the ER-mitochondria unit, leading to a decrease in intra-mitochondrial calcium, activity of Ca^{2+}-sensitive mitochondrial enzymes (pyruvate dehydrogenase) and increased mitochondrial membrane potential, all resulting in increased proliferation and suppressed apoptosis in PASMCs. $Rtn4^{-/-}$ mice, but not wildtype controls, were resistant to chronic hypoxia-induced PAH measured by invasive hemodynamics, PA vascular remodeling, right ventricular hypertrophy and exercise capacity. 4-Phenylbutyrate (PBA), a clinically used chemical chaperone that inhibits ER stress, prevented induction of Rtn4 in vitro and both prevented and reversed established PAH in rats.
CONCLUSION: Pulmonary circulation-selective induction of Rtn4B may initially disrupt the ER-mitochondria unit and suppress apoptosis, rescuing PASMCs from death during ER stress, at the expense of eventual development of PAH. Attenuating ER stress with PBA may represent a novel therapeutic approach with rapid translational potential.

Metabolic Regulation of Nuclear Histone Acetylation

Sutendra G, Dromparis P, Stenson TH, Da Silva A, Haromy A,
McMurtry MS and Michelakis ED

INTRODUCTION: Epigenetic traits in cancer are regulated in part, by histone acetylation, a major mechanism for global gene regulation. Histone deacetylase (HDAC) inhibitors are novel anti-cancer drugs but limited by a lack of selectivity for cancer cells. Metabolic modulation with dichloroacetate (DCA) selectively changes the global genetic profile of cancer cells, suggesting that metabolism may affect histone function. Since DCA increases mitochondrial metabolism, the center for acetyl-CoA synthesis (the substrate for acetylation processes), we hypothesize that histone acetylation is linked to mitochondrial function.

METHODS/RESULTS: In human non-small cell lung cancer cells (NSCLC), DCA increased mitochondrial pyruvate dehydrogenase activity and acetyl-CoA levels (ELISA) compared to vehicle ($p<0.001$). In both, whole cell preparations and purified nuclear histone extractions from NSCLCs, DCA increased histone-3 (H3) acetylation (immunoblots, ELISA) to levels similar to non-cancerous small airway epithelial cells. To correlate mitochondrial activity with histone acetylation, we used two mammary carcinoma cells lines with differing levels of mitochondrial activity, due to high vs. low levels of the metabolic transcription factor p53. $p53^{HIGH}$ had higher mitochondrial activity and H3-acetylation compared to $p53^{LOW}$ cancer cells. DCA increased H3-acetlyation in both. *In-vivo*, athymic rats injected with NSCLC and treated with DCA (70mg/kg/day) had significant H3-actelyation resulting in an 85% reduction in tumor size. Similar results were obtained in three patients with glioblastoma in a U of A clinical trial where tumor tissues were compared before and after oral DCA therapy.

CONCLUSIONS: We show that DCA increases histone acetylation, potentially normalizing the epigenetic traits of cancer cells, by increasing mitochondrial activity and acetyl-CoA levels. Because DCA is relatively selective to cancer cells, this novel way of modifying histone acetylation may overcome the lack of selectivity of otherwise effective HDAC inhibitors.

A Metabolic Basis for RV angiogenesis

Sutendra G, Dromparis PR, Stenson T, Haromy A,
McMurtry MS and Michelakis ED

INTORDUCTION: In pulmonary arterial hypertension (PAH), after a short compensatory phase, the right ventricle (RV) decompensates by an unknown mechanism; decreased angiogenesis may play a role. Mitochondria, which regulate cell metabolism and O2 sensing, can directly inhibit HIF-1α (and thus angiogenesis) by mitochondrial reactive oxygen species (mROS) and by providing prolyl-hydroxylases substrates (α-ketoglutarate). The glycolytic environment in cancer (even under normoxia) is associated with HIF activation. Since the hypertrophied myocardium is also glycolytic, we hypothesized that a metabolic remodeling might regulate angiogenesis and mark the transition from a compensated RV (CRV) to a decompensated RV (DRV).

METHODS/RESULTS: We studied serial RV mitochondrial/HIF-1α activity and angiogenesis in monocrotaline (MCT)-induced PAH rats, where the first 3wks are characterized by CRV, with increased morbidity and mortality (DRV function) beginning at 4 and peaking at 6wks. PAH (decreased PA acceleration time) was associated with RV hypertrophy (RV/LV+Septum). Compared to control, CRV (2-3 wks-MCT) exhibited increased mitochondrial potential (TMRM), decreased mROS (MitoSOX), decreased α-ketoglutarate, activation of HIF-1α (immunohistochemistry), increased expression of HIF-1α regulated chemokines (VEGF, SDF1), increased ckit+ stem cell recruitment and increased RV glucose uptake (in vivo PET). This resulted in increased RV capillary density (Lectin). In 6wk-MCT (DRV) there was increased mROS, decreased HIF-1α activity, and decreased capillary density, compared to CRV. Uncoupling protein-2 (UCP2), which increases mROS by uncoupling mitochondria, was induced at 4 wks, potentially explaining the disruption of the pro-angiogenic metabolic response and the suppression of HIF and angiogenesis.

CONCLUSIONS: The UCP2-promoted decreased capillary density in the setting of persistent RVH may explain the RV failure due to ischemia.

Table 1	**Control (n=5)**	**2/3wks MCT (n=7)**	**4/5wks MCT (n=5)**	**6wk MCT (n=5)**
PAAT (Sec)	0.037±0.0004	0.025±0.001*	0.013±0.0009*	0.013±0.0007*†
RV/LV+Septum (%)	26±0.9	31±2*	63±1*	58±1*†
ΔΨm (AFU)	8±0.2	12±0.4*	15±0.7*	13±0.7*
mROS (AFU)	86±4	67±2*	54±3*	81±4†
PET (FDG18; RV/LV)	38±4	52±3*	72±5*	53±4*
SDF/Actin	0.17±0.005	0.33±0.06*	0.37±0.04*	0.28±0.04*†
VEGF/Actin	0.86±0.06	1.05±0.03*	1.08±0.06*	0.77±0.1*†
ckit/Actin	0.72±0.07	0.99±0.09*	1.44±0.08*	0.67±0.05†
UCP2/Actin	0.5±0.02	0.56±0.03	1.01±0.08*	1.23±0.06*†
Lectin Density	9±1	28±3*	17±4*	12±2*†

*p<0.01 vs. Control, †p<0.01 vs. 2/3wk MCT

THE PUBLIC HEALTH CONSEQUENCES OF SMEAR POSITIVE PULMONARY TUBERCULOSIS IN PATIENTS WITH TYPICAL OR ATYPICAL CHEST RADIOGRAPHS

Lau A, Barrie J, Winter C, Kunimoto D, Elamy H, Tyrrell G, Long R

INTRODUCTION: Using currently available digital technology, it should be possible to automate the detection of 'typical' post-primary tuberculosis (TB) on chest radiograph (CXR). Development of such a detection system is warranted if it can be demonstrated that patients with 'typical' (vs 'atypical') CXRs are responsible for most public health consequences (recently infected persons amongst close contacts; secondary cases amongst all cases).

METHODS: Over 30 months beginning January 1, 2006, all adults (age >14 years) diagnosed with smear-positive pulmonary TB in Alberta, were identified in the TB Registry. Patient demographics and mycobacteriology were abstracted from public health records and the Provincial Laboratory for Public Health. Pre-treatment posterior-anterior and lateral CXRs were assembled and scored by 3 independent readers as 'typical' (having an upper lung zone infiltrate, with or without cavitation, but no discernable intrathoracic adenopathy) or 'atypical' (all others). The public health consequences, confirmed using molecular diagnostics, from each group were compared.

RESULTS: There were 88 adults with smear-positive pulmonary TB, of whom 62 (70.5 %) had a 'typical' CXR. Patients with 'typical' CXRs had, on average, larger bacillary burdens and metabolically more active bacteria (larger semi-quantitative smears; shorter times-to-culture-positivity) than patients with 'atypical' CXRs. More importantly, they were responsible for most public health consequences: 0.39 vs 0.04 child-aged tuberculin skin test (TST) converter per source case, p=0.008; 0.83 vs 0 child-aged TST converter per Canadian-born source case, p=0.009; and 35 vs 4 secondary cases (51.3% were type 1 [identified by conventional epidemiology, confirmed by molecular epidemiology], 25.6% were type 2 [identified by conventional epidemiology, unconfirmed by molecular epidemiology], and 23.1% were type 3 [identified by molecular epidemiology and linked to the source case spatially and temporally]).

CONCLUSIONS: Adult smear-positive pulmonary TB patients with 'typical' CXRs are responsible for most public health consequences. Accordingly, the development of an automated TB detection system is warranted.

SUPERVISOR: Dr. Richard Long

Transcription of *CRTh2* (Chemoattractant Receptor homologus molecule expressed on Th2 cells), a gene involved in allergic inflammation, is regulated by GATA3

MacLean E, Tse C, Davidson C, Campos E, Vliagoftis H and L Cameron

Pulmonary Research Group, Department of Medicine, University of Alberta, Edmonton, Canada

INTRODUCTION: Allergic inflammation is mediated by T helper 2 (Th2) cells. CRTh2 is expressed by Th2 cells and mediates chemotaxis and production of the Th2 cytokines IL-4, IL-5 and IL-13. In an effort to understand the molecular regulation of CRTh2, we studied the promoter sequence and identified putative binding sites for GATA3 and NFAT, transcription factors known to regulate Th2 cytokine gene expression. *We hypothesize these factors also regulate transcription of CRTh2*.

METHODS: A luciferase reporter construct containing 450 base pairs 5' of exon 1 (CRTh2-450/Luc) was transiently transfected into primary *in vitro* differentiated Th2 cells ($CRTh2^+$) or non-polarized $CRTh2^-$Th cells (Jurkat) and cultured overnight ± mitogenic stimulation. Transcription factor binding was assessed by electromobility shift assays (EMSA) using an oligonucleotide probe representing –94/-125 of the CRTh2 proximal promoter. The effect of transcription factors, GATA3, NFAT1 and NFAT2 on promoter activity were assessed by over-expression in $CRTh2^-$ cells co-transfected with the CRTh2-450/Luc reporter construct.

RESULTS: Th2 cells ($CRTh2^+$) showed a significantly higher fold-induction of CRTh2 proximal promoter activity than non-polarized $CRTh2^-$ cells ($p<0.05$). EMSA analysis with nuclear extracts from $CRTh2^+$ Th2 cells showed binding of GATA3 without stimulation and binding of NFAT1 following mitogenic stimulation. Over-expression of GATA3 in $CRTh2^-$ cells increased CRTh2-450/Luc promoter activity to levels seen in $CRTH2^+$ cells, while over-expression of NFAT1 interfered with GATA3 mediated promoter activity.

CONCLUSIONS: The Th2 nuclear environment provides a distinct complement of transcription factors supporting robust activation of CRTh2 transcription. Studying the molecular mechanisms underlying regulation of CRTh2 will lead to a better understanding of the development of Th2 immunity and allergic disease.

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TITLE: COMPARISON OF ACTUAL WAIT TIMES OF UNIVERSITY OF ALBERTA GASTROENTEROLOGY OUTPATIENTS TO PUBLISHED CANADIAN ASSOCIATION OF GASTROENTEROLOGY MAXIMAL ACCEPTABLE WAIT TIMES

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PRESENTATION TYPE: Poster/Oral

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ABSTRACT BODY:
Aims: The aims of this study were to analyze wait times for 4 indications of referrals received at the University of Alberta (UofA) GI Division: Rectal Bleeding (RB), Iron Deficiency Anaemia (IDA), FOBT+ Stool (FOBT), and Abdominal Pain (AP) in order to determine 4 outcomes: 1) the frequency of referrals, 2) acuity 3) Decline (Dec.) rates, and 4) wait times to endoscopic procedures. The 4th outcome was used to make a comparison to recommended published guidelines of the Canadian Association of Gastroenterology (CAG). Accepted CAG wait times are 8 weeks for all 4 indications. Our hypothesis was that > 25% of referrals received by the UofA GI Division, and classified as any of the 4 indications studied, exceeded CAG acceptable wait times by at least 4 weeks.

Methods: All requests for GI outpatient referrals were categorized according to 40 indications, acuity level (Emergent, Urgent, Semi-Urgent, Non-Urgent) and entered in a central electronic database, which now contains over 4000 patients. Approximately 30% of all referrals are rejected using six standardized reasons for rejection, e.g. unable to see in a timely fashion, patient was seen in last 5 years by other GI physician. GI outpatient referral information (Jan 1, 2010 to July 30, 2010) was retrieved from this database for patients referred for RB, IDA, FOBT and AP indications. Parameters used to calculate wait times (wks) and acuity distributions, by indication, included: date referral was received, date of booked clinic appointment, date of booked endoscopy appointment and triaged acuity level. Wait times to “endoscopy only”, “post-clinic-endoscopy” and “clinic only” GI appointments were calculated.

Results : 909 referrals, of the 4 indications studied, were received and triaged at the UofA GI Division between Jan-July, 2010: RB (N=207; 35.7% Dec.), IDA (N=109 41.7% Dec.), FOBT (N=104; 41.3% Dec.), AP (N=489; 63.8% Dec.). Table 1 indicates acuity distributions and median wait time (wks) to GI appointments, as well as % of wait times exceeding CAG targets, by indication.

Conclusions: Median wait times for the 4 indications exceeded the consensus target. Between 42.8-58.2% of clinic or endoscopy patients were not seen within 8 weeks. Currently, UofA’s GI Division is not meeting the outpatient consultation demand as the rejection rate is high and for those that are seen the accepted wait times are exceeded for 53.8 % of patients.

Table 1: Acuity Distribution and Wait Times to GI Appointment by Indication

Indication	N (Accepted)	No Acuity Data (%)	Emergent (%)	Urgent (%)	Semi-Urgent (%)	Non-Urgent (%)	Acuity N/A (%)	Median Wait To Endo Only (wks)	Median Wait to Post-Clinic Endo (wks)	Median Wait to Clinic Only (wks)	% > CAG Maximum Wait Time
RB	133	0.78	4.52	8.99	51.1	32.3	2.23	10	9	10	55.67

IDA		1.54	4.69	20.33	45.30	28.14	0	7	9	9	48.43
FOBT	61	0	1.66	14.79	52.46	27.86	3.3	9	15	7	42.8
AP	177	0	0.56	3.39	41.78	52.56	1.66	8	12	11	58.17

(No Image Selected)

SUPPLEMENTAL DATA: none

Influence of cholesterol accumulation on APP and Aβ metabolism

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INTRODUCTION: Evidence suggests that cholesterol can influence the generation of β-amyloid (Aβ) peptide, the key player in Alzheimer's disease pathogenesis, by regulating amyloid precursor protein (APP) processing. However, most of these observations arise either from cell culture studies using drugs having multiple effects or animal models with dietary modulation of cholesterol, which does not cross the blood-brain barrier. At present, it remains unclear how cells/neurons genetically modified to accumulate cholesterol can influence APP processing and Aβ production. To address this issue, we developed novel *in vitro* and *in vivo* genetic models overexpressing APP in the absence of Niemann-Pick type C1 (Npc1) protein, required for intracellular cholesterol transport, and analyzed the effects of cholesterol accumulation on APP/Aβ metabolism.

METHODS: A novel transgenic (Tg)-line (*APP*$^{+/-}$*/Npc1*$^{-/-}$) has been developed by crossing mutant APP-Tg mice with Npc1-deficient mice. We have also developed a stable mouse neuroblastoma cell line (N2a) overexpressing APP and with Npc1depletion mediated by Npc1-shRNA lentiviral particles. Using both the animal model and cell culture paradigms we studied cholesterol accumulation and its influence on alterations in the levels of APP/Aβ, and their biosynthetic and degrading machinery by real-time PCR, western blotting, ELISA and confocal microscopy.

RESULTS: *APP*$^{+/-}$*/Npc1*$^{-/-}$ mice have a reduced life-span along with exacerbated cognitive/motor impairments and neuropathological abnormalities. Biochemical assays revealed that intracellular cholesterol accumulation in brain neurons of *APP*$^{+/-}$*/Npc1*$^{-/-}$ mice and in cultured N2a cells can differentially regulate APP, APP C-terminal fragments (CTFs) and Aβ40/42 levels with no evident alterations in APP mRNA levels. In addition, components of the APP processing machinery were elevated suggesting a role of these enzymes in regulation of Aβ levels.

CONCLUSIONS: Our results demonstrate that intracellular cholesterol sequestration can regulate the production/accumulation of Aβ and APP CTFs which can influence neuronal viability.

SUPERVISOR: Dr. Satyabrata Kar

Patients Undergoing Colorectal Cancer Screening Underestimate Their Skin Cancer Risk and Delay Presentation for Screening

Nicholas Gies, Haili Wang, Clarence Wong, Dan Sadowski, Richard N Fedorak

INTRODUCTION: CRC screening guidelines state that first-time screening should occur at age 50 for average-risk individuals and at age 40 for those with a family history (FH) of CRC. This study examines whether persons with a positive CRC FH or no CRC FH are achieving screening at the correct ages. A secondary objective was to determine whether the CRC screening is self-initiated or physician-initiated

METHODS: This study is a cross-sectional analysis of subjects from the Edmonton, Alberta SCOPE (Stop COlorectal cancer through Prevention and Education) study who were undergoing CRC screening for the first time. Each subject was mailed a questionnaire consisting of questions to determine how their screening was initiated and their reasons for seeking CRC screening.

RESULTS: There were a total of 778 individuals enrolled in this study; 438 had a positive CRC FH and 340 did not. For the group with a positive CRC FH the average age for primary screening was 54.4 years (SD=8.5), compared to 58.2 years (SD=6.4) for the group with no CRC FH. Those with a positive CRC FH initiated screening 3.8 years (95% CI 2.8-4.8, $p<0.05$) earlier than those without, however subjects with a positive CRC FH started their screening 14.4 years later than recommended and subjects with no CRC FH were starting 8.2 years later than recommended. Only 43.8% of the positive CRC FH group rated their own risk appropriately in the above average risk category. Of the no CRC FH group only 57.3% rated their risk appropriately in the average risk category. In the no CRC FH group, 28.6% self-initiated the screening process, whereas in the positive CRC FH group, 35.6% did.

CONCLUSIONS: Both groups are getting their screening well past the age suggested by current guidelines. Although subjects with a positive CRC FH were more likely to self-initiate the process of screening, it was clear that most of them did not realize they were in the above average risk category for development of CRC.

SUPERVISOR: Richard N Fedorak

The Effect of Performance-Based Remuneration on Clinical, Economic, and Quality Outcomes in Health Care – A Systematic Review

Houle SK, Jackevicius CA, McAlister FA, Chuck AW, Tsuyuki RT

INTRODUCTION: Payment for professional services represents a significant proportion of healthcare costs. As a result of rising costs and increased demand for services, there is interest in investigating innovative remuneration models in an effort to control costs and improve quality of care. The objective of this study is to systematically review the literature comparing the performance-based remuneration to other remuneration models on clinical, economic, and quality outcomes.

METHODS: Systematic search of PubMED, MEDLINE, EMBASE, The Cochrane Library, OpenSIEGLE, Canadian Evaluation Society Unpublished Literature Bank, and the New York Academy of Medicine Library Catalogue from their inception until March 2011 for remuneration, economic, and clinical terms. Included studies were original research papers comparing at least 2 remuneration models and reporting on clinical, economic, or quality outcomes.

RESULTS: 76 articles met the inclusion criteria, 18 of which included performance-based remuneration as one of the comparison groups. All but 4 of the 18 performance-based remuneration papers were observational. Included studies were of highly varying methodology and quality and assessed different outcome measures, precluding the use of meta-analysis. Some evidence of improved vaccination rates in children and seniors were noted, as well as some improvement in adherence to quality measures. However, performance-based remuneration was not demonstrated to have an effect on hypertension outcomes or preventive practices in adult patients, and reductions in patient care costs observed in another study were not statistically significant.

CONCLUSIONS: There is insufficient evidence on the merits of performance-based remuneration within health care and its cost implications across different care settings and disease states. Short study durations, variable study quality, and poor external generalizability of existing research precludes the formation of solid conclusions on the long-term effects of performance-based remuneration and its applicability across various healthcare settings.

SUPERVISOR(S): Ross Tsuyuki, BSc(Pharm), PharmD, MSc

Characterization of the aberrant translocation of PDC-E2 in primary biliary cirrhosis.

Gilady, Susanna

INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease that predominantly affects women. Central to this disease is the aberrant expression of a protein to the cell surface that is under normal conditions found within the inner mitochondrial membrane. This disease-specific exposure of PDC-E2 causes the breakdown of self-tolerance and the production of auto-mitochondrial antibodies (AMAs) which are detected in the serum of asymptomatic and symptomatic PBC patients. Disease manifestations include the destruction of the small intrahepatic bile ducts leading to a dramatic build-up of bile within the liver. This damage correlates with the drastic lymphoid infiltration of the liver tissue, resulting in fibrosis, cirrhosis and ultimately liver failure. Currently, there is only one FDA-approved therapy to treat PBC patients: ursodeoxycholic acid (UDCA) which cannot inhibit nor cure the progression of PBC. In fact, UDCA exclusively prolongs the progression of PBC, consequently resulting in liver failure. Recent findings demonstrated the presence of a novel retrovirus, known as the human betaretrovirus (HBRV) in perihepatic lymph nodes of PBC patients. Intriguingly, HBRV has a 95% nucleotide homology with the mouse mammary tumor virus (MMTV). It remains to be elucidated whether HBRV-infection initiates PDC-E2 to be translocated out of mitochondria.

METHODS

Primary biliary epithelium was obtained from explanted livers from patients with various liver diseases at the UAH. Optiprep-gradients were performed as described in Gilady *et al.* (2010). Mitochondrial purifications were performed using the 'Mitochondria Isolation Kit' (Thermo Scientific).

RESULTS

The results show the translocation of PDC-E2 away from mitochondria. Moreover, an increase of AMA at the protein level is observed in PBC BECs as well as in HEK293s transfected with MMTV-Hybpro.

CONCLUSIONS

The aberrant expression of PDC-E2 to the cell surface of biliary epithelium is a hallmark of PBC; however the underlying mechanism of this peculiar translocation remains to be elucidated. Therefore, this project aims to identify the mechanism of translocation of the mitochondrial-resident protein, PDC-E2.

SUPERVISOR: Dr. Andrew Mason

Loss of apelin results in reduced cardiac function recovery from ischemia-reperfusion injury

Wang W., G. Y. Oudit

INTRODUCTION Apelin, the endogenous ligand of APJ, was reported to protect the heart from ischemia-reperfusion (IR) injury when given at the beginning of reperfusion but not before ischemia. Mechanism involved in such a protection is not fully understood while has been attributed to the reperfusion injury salvage kinase (RISK) pathway, activation of superoxide dismutase. To get a further understanding of the role of apelin, especially as post-conditioning tool, in the protection of IR, we employed wild type and APLN knockout mice. An exacerbated cardiac functional recovery from IR injury is expected in APLN KO mice compared to WT. METHODS Langendorff perfused C57Bl/6 or APLN KO mouse hearts were subjected to 30 min global ischemia followed by 40 m in reperfusion. Hear rate (HR), left ventricular developed pressure (LVDP), left ventricular end of systolic pressure (LVESP), Max dP/dt, Min dP/dt (±dP/dt), rate-pressure product (RPP) were recorded to estimate the cardiac function of each group. RESULTS Functional recovery was significantly decreased in APLN KO hearts with LVDP averaging 33.85 mmHg (WT) versus 19.52(APLN KO) P< 0.05 versus control at the end of 40min's reperfusion; LVESP averaging 98.73 mmHg (WT) versus 83.46 mmHg(APLN KO) P< 0.05 ve rsus control; max dP/dt averaging 1288.58 mmHg/s (WT) versus 609.62 mmHg/s(APLN KO) P< 0.05 versus control; min dP/dt averaging -539.10 mmHg/s (WT) versus -329.11 mmHg/s(APLN KO) P< 0.05 versus control; RPP averaging 9975.03BPM*mmHg (WT) versus 4208.21 BPM*mmHg (APLN KO) P< 0.05 ve rsus control. CONCLUSIONS Apelin deficiency in mice exacerbates ischemia-reperfusion injury. SUPERVISOR Dr. Gavin Y. Oudit.

Potential role of IGF-II receptor in the regulation of APP processing

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INTRODUCTION

The insulin-like growth factor-II (IGF-II) receptor is a multifunctional glycoprotein involves in the transport of newly synthesized lysosomal hydrolases from the trans-Golgi network to endosomes. Accumulated evidence suggests that the endosomal-lysosomal system, the major site of IGF-II receptor expression, plays a critical role in the processing of amyloid precursor protein (APP) leading to the generation of β-amyloid (Aβ) peptide - a key player in the development of Alzheimer's disease pathogenesis. However, the potential role of the receptor in APP processing remains unclear. To address this issue we used wild-type and IGF-II receptor knock-out fibroblast cell lines to measure the influence of the receptor on APP levels and its processing leading to generation of Aβ peptides.

METHODS

Wild-type and IGF-II receptor knock-out mouse fibroblast cell lines were cultured in DMEM and then processed using AD-related PCR-Arrays to detect the mRNA levels of markers involved in APP processing. Subsequently, we used western blotting, ELISA and confocal microscopy to measure the levels and distribution of APP, its processing enzymes and Aβ peptides.

RESULTS

Our PCR array data reveal lower levels of APP mRNA but higher levels of some APP secretases mRNAs in IGF-II receptor knock-out cells compared to wild-type cells. In accordance with our PCR array data, we observed a decrease level of APP holoprotein and increase levels of β- and γ-secretases in IGF-II receptor knock-out cells. The levels of secreted N-terminal APP fragment as well as $A\beta_{1-40}$ and $A\beta_{1-42}$ are lower in the conditioned media of IGF-II receptor knock-out cells. Additionally, the levels of β-C-terminal APP fragment, the immediate precursor of Aβ peptides, were found to be lower in IGF-II receptor knock-out cells.

CONCLUSIONS

These results suggest that lower IGF-II receptor level can lead to decreased levels of APP mRNA/protein along with decreased secretion of Aβ peptides.

SUPERVISOR

Dr. Satyabrata Kar

Role of IL-33 in Central Nervous System Immunomodulation

Diane Turner, Beipei Shi, Fabrizio Giuliani

INTRODUCTION: Multiple Sclerosis (MS) is an inflammatory, demyelinating autoimmune disease with a neurodegenerative component. The hypothesized mechanism for MS is a myelin specific T helper (T_H) 1 cell-mediated response resulting in myelin sheath damage and axonal death. We have previously shown that T_H1 cells induce neuronal killing while T_H2 cells are neuroprotective. Shifting the balance from T_H1 to T_H2 is beneficial for MS patients and a current therapeutic strategy. However, stronger therapeutic techniques are required. Helminthic infections are the strongest natural activators of T_H2 responses. Helminths induce a T_H2 cytokine upregulation, specifically interleukin (IL)-33. We hypothesize that IL-33 is able to induce a significant T_H2–polarized environment and subsequent neuroprotection from an inflammatory insult.

METHODS: We isolated CD4+ T_H cells from peripheral blood mononuclear cells and co-cultured them with neuronal cell lines or primary human neurons in the presence or absence of IL-33.

RESULTS: Our results demonstrated that IL-33 has a neuroprotective effect in neuronal cell lines at lower concentrations (10 ng/ml), while higher doses increased neurotoxicity.

CONCLUSION: IL-33 is a powerful mediator of T cell polarization and can be effectively used to shift the immune system towards a neuroprotective phenotype. These results suggest a new therapeutic strategy for MS patients.

Irinotecan (CPT-11) chemotherapy and oral glutamine alter colonic microbiota in tumor bearing rats

XiaoXi B. Lin, Levinus A. Dieleman, Ali Ketabi, Ilona Bibova, Michael B. Sawyer, Hongyu Xue, Catherine J. Field, Vickie E. Baracos, Michael G. Gänzle

INTRODUCTION

Irinotecan (CPT-11) treatment for cancer produces toxic side effects, especially late-onset diarrhea. Intestinal microbiota species are potential mediators of this toxicity as well as agents causing systemic infection after CPT-11-induced loss of barrier function.

METHODS

We used a combination of qualitative and quantitative taxonomic and functional analysis to characterize the responses of intestinal microbiota to two CPT-11-based regimens, in presence or absence of oral bolus glutamine, a treatment we previously showed to mitigate CPT-11 toxicity. In a dose-intensive regimen, tumor bearing rats received CPT-11 (125 mg/kg × 3 days), with or without oral glutamine bolus (0.75 g/kg). In a clinically-oriented regimen rats received two cycles of CPT-11 (50 mg/kg) followed by 5-flurouracil (50 mg/kg).

RESULTS

The numbers of colonic *Clostridium* cluster XI and *Enterobacteriaceae* spp. were increased with both regimens, with changes of a larger magnitude using the dose intensive therapy. The dose intensive regimen also reduced the abundance of bifidobacteria and the *Lactobacillus* group. In addition, CPT-11 therapy induced bacterial translocation to the mesenteric lymph nodes, notably species of the *Enterobacteriaceae* family, enterococci and staphylococci. Virulence factor/toxin genes of enteric pathogenic *Escherichia coli* and *Clostridium difficile* were not detected in the cecal microbiota and translocated bacteria. Glutamine partially mitigated changes to intestinal microbiota 6 h after CPT-11 administration, but those effects were no longer significant after 7 days.

CONCLUSIONS

CPT-11-based chemotherapies caused major disruption in intestinal microbiota, and bacterial translocation. Glutamine partially mitigated the early changes of CPT-11-based chemotherapy.

SUPERVISOR

Dr. Michael G. Gänzle

Regulatory effects of microRNAs on brain-derived HIV-1 Vpr expression
Hui E, Ellestad K and Power C

INTRODUCTION: Regulation of gene expression by microRNAs (miRNAs) is based on complementary base-pairing of targeted messenger RNAs, which are subsequently degraded or translationally repressed. The non-structural human immunodeficiency virus 1 (HIV-1) encoded protein, viral protein R (Vpr), participates in multiple aspects of HIV-1's pathobiology. We hypothesized that select cellular miRNAs modulated HIV-1 gene expression by targeting, *vpr*.

METHODS: A microRNA array comparing HIV encephalitis (HIVE) with non-HIV-infected brains detecting differentially expressed microRNAs was used together with bioinformatic analyses to determine potential HIV-1 *vpr* mRNA target sites. To evaluate the impact of these miRNAs on Vpr, several Vpr-expressing clones were examined: vpr_{NL4-3}, Vpr with R77Q, vpr_{NL4-3D}, a brain-derived *vpr* clone from a person with HIV-associated dementia (HAD), vpr_{HAD}, and a brain--derived *vpr* clone from a person with AIDS but not demented (ND), vpr_{ND}. Co-transfections of HEK 293T cells with target clones and select microRNAs were used to determine their effects on *vpr* gene and protein expression using real time RT-PCR and a dual *Renilla*/firefly luciferase vector.

RESULTS: MicroRNA array analyses and bioinformatic analyses disclosed specific microRNAs, miR-149 and miR-211, were predicted to target *vpr* in the brain. A reduction in *vpr*-encoding RNA expression was observed in 293T cells co-transfected with miR-149 and each *vpr* clone (in all cases, $p \leq 0.001$); however, only cells co-transfected with Vpr_{NL4-3D} or Vpr_{ND} and miR-211 showed a reduction in *vpr* transcript abundance ($p \leq 0.01$ and $p \leq 0.05$, respectively). Vpr protein expression was reduced following co-transfection with miR-149 and Vpr_{NL4-3}.

CONCLUSIONS: These data suggest a role for miR-149, and possibly miR-211, in modulating the expression of different *vpr* alleles and underscore the ability of Vpr to direct cellular processes, which exert important effects on viral replication and pathogenesis.

SUPERVISOR(S): Power C

Abstract Unavailable

NT2 cell line as an *in vitro* Model for The Study of Neurodegenerative Diseases: Comparison with Human Fetal Neurons

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INTRODUCTION: The goal of this study is to develop neuronal cell-lines as a model for the investigation of inflammation-mediated neuronal injury in neurodegenerative diseases such as multiple sclerosis (MS). MS is the most common cause of non-traumatic chronic neurological disability affecting young adults. MS is characterized by demyelination and neurodegeneration. Despite the implication of inflammatory cells in neuronal degeneration in MS, the underlying mechanisms are unclear. To address this question, we established an *in vitro* cell culture system using primary human fetal neurons (HFNs). However, the availability of HFNs is unpredictable and severely hampers the progress of the studies. To mitigate this issue, we differentiated human neuronal cell lines from human teratoma stem cells (NT2) and evaluated the maturity and physiological properties of the cell-lines in comparison to the primary neuronal cells.

METHODS: NT2 cells were cultured on T 75 flasks supplemented with DMEM + FBS; and differentiated to neurons by treating with retinoic acid for 4 weeks. HFNs were isolated from the brain tissue of 15-20 week-aged fetuses. The maturity and viability NT2 and HFNs was assessed using immunocytochemistry for microtubule associated protein-2. The physiological property of HFNs and NT2 cells was evaluated by patch clamping. Parameters such as neurite length, cell size and nuclear area of the cells was analysed by In-cell Western.

RESULTS: The findings showed that treatment of teratoma stem cells with retinoic acid induce mature NT2 neurons. These teratoma cells-derived neurons have significantly longer neurites, bigger nuclear size, larger area of the whole cell and cell body compared to the primary human neurons. The action potential of NT2 was similar to HFNs.

CONCLUSION: This study shows NT2 neurons are bigger in morphology but similar in physiological property to HFNs. This is encouraging to use the readily available NT2 cell-lines as *in vitro* model to study neurodegenerative diseases.

Histamine induces the production of Matrix Metalloproteinase-9 in cultured rat astrocytes

Patel AN, MacTavish D, Jhamandas JH

INTRODUCTION:
β-amyloid (Aβ) accumulation and neuritic plaque formation in the brain are major neuropathological hallmarks of Alzheimer's disease (AD). One of the strategies proposed to alter the Aβ deposition in the brain is promotion of Aβ catabolism. Matrix Metalloproteinase-9 (MMP-9) is one of the potential Aβ-degrading enzymes and a member of the family of Zn^{+2} containing endoproteases. Astrocytes in close proximity to Aβ plaques produce MMP-9, which has been shown to effectively degrade Aβ. Interestingly, histamine, a major aminergic neurotransmitter in the brain, has been shown to stimulate the production of MMP-9 in keratinocytes through histamine H1 receptor. Based on these observations, we hypothesized that histamine-evoked increase in MMP-9 release from astrocytes may promote potentially beneficial clearance of Aβ deposits in the brain.

METHODS:
Primary rat astrocyte cultures were established and exposed to different concentrations of histamine (1-100μM range) for varying lengths of time (24-72h). MMP-9 levels in conditioned culture media were measured using standard gelatin zymography methods.

RESULTS:
Quantitative analysis of gelatin zymograms, revealed histamine increased the production of pro-MMP-9 by astrocytes, in a dose- and time- dependent manner. However, levels of pro-MMP-2 remained unchanged.

CONCLUSION:
Histamine induces an increase in MMP-9 release from astrocytes, which in turn could increase Aβ clearance through as yet unknown mechanisms. In future studies, we aim to determine identity of histamine receptor(s) that might be involved in mediating the increased release of MMP-9 using specific antagonists for histamine receptor sub-types (H1, H2 and H3). We further plan to investigate cellular and molecular mechanisms whereby MMP-9 may have neuroprotective effects against Aβ toxicity.

SUPERVISOR:
Prof. Jack H Jhamandas

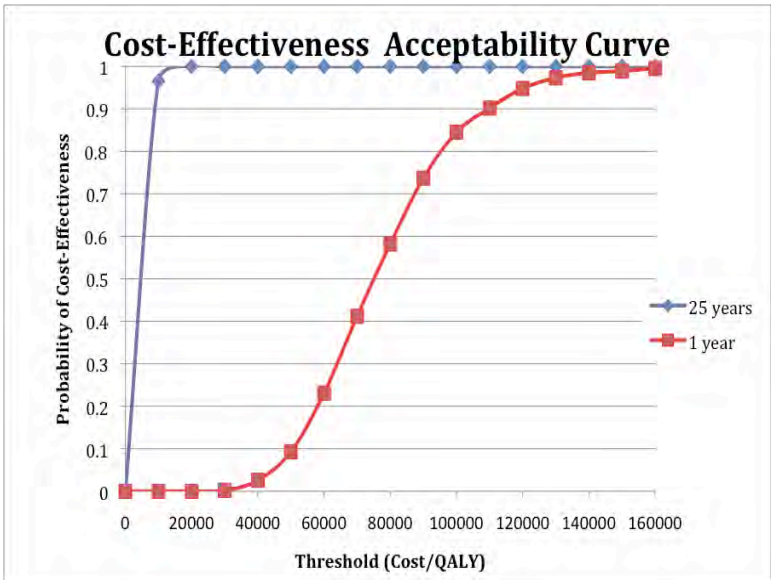
ECONOMIC EVALUATION OF ERYTHROPOIESIS STIMULATING AGENTS IN CRITICALLY ILL TRAUMA PATIENTS

Chui BK, Hazel M, Dong J, Klarenbach SW

INTRODUCTION: Recent randomized trials (RCT) have suggested erythropoiesis stimulating agents (ESA) reduce mortality in critically ill trauma patients; however ESA are associated with adverse effects and are costly. We sought to determine cost-effectiveness of ESA in this patient population.
METHODS: A decision analytic model was constructed to compare the use of ESA to standard care in trauma patients admitted to an intensive care setting. Base case costs and benefits at one year were estimated using mortality estimates from available RCTs. One way and probabilistic sensitivity analyses were conducted for comparison of the base case scenario with 10 and 25 year time horizons in Markov models.
RESULTS: ESA was associated with a cost per quality adjusted life year (QALY) gained of $74,500 compared with standard care at one year. One-way sensitivity analyses indicated results were sensitive to risk and relative risk of mortality, risk and relative risk of thrombosis, and quality of life estimates. Cost effectiveness acceptability curves generated from probabilistic sensitivity analysis indicated that the probability ESA would be considered attractive ranged from 35% to 80% over willingness to pay thresholds of $60,000/QALY to $120,000/QALY. Consideration of 10 and 25 year time horizons reduced the cost per QALY gained to $9,338 - $5,957. Sensitivity analyses using a 25 year time horizon model were found to be robust with the exception of the relative risk of mortality.
CONCLUSIONS: While the cost per QALY gained with ESA use falls into the range of currently accepted healthcare technologies funded in Canada, significant uncertainty exists, particularly long-term survival benefit with ESA use. Further research into the efficacy and safety of ESA use in critically ill trauma patients is required prior to widespread use.

Table 1: Base case analysis – one year time horizon

Strategy	Cost	Incr Cost	Effect	Incr Effect	ICER (Cost/QALY)
Standard Care (transfusion therapy)	36,192		0.627		
ESA + Standard Care	37,937	1,745	0.651	0.023	74,500



Angiotensin converting enzyme 2 (ACE2) deficiency results in endothelial dysfunction and worsens diabetic cardiomyopathy

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INTRODUCTION: Incidence of heart disease and severity of heart failure is high in diabetic, than the non-diabetic. This increased risk appears to be due to hyperglycemia-stimulated cardiac angiotensin II formation, which has been implicated in increased cardiac dysfunction. Angiotensin converting enzyme 2 (ACE2) is a homolog of the ACE that breaks down Ang II to Ang 1-7, that has the capacity to counter the actions of Ang II.

METHODS: To better define the role of ACE2 in diabetic cardiovascular complications, we examined cardiac and vascular function by echocardiography, hemodynamics and molecular signaling in male mice with genetic ablation of ACE2 in the context of the Akita model of type 1 diabetes.

RESULTS: Type 1 diabetic cardiomyopathy in the Akita mouse model was characterized by lipotoxicity and diastolic dysfunction with preserved systolic function. Myocardial ACE2 levels were increased in the diabetic Akita mice. ACE2 deficient mice did not exhibit any signs of cardiac dysfunction. However, superimposing ACE2 deficiency in Akita mice (model of type I diabetes) resulted in systolic dysfunction, with elevated filling pressures, with restrictive diastolic filling pattern. Hyperglycemia together with ACE2 deficiency enhanced protein kinase C-dependent activation of NADPH oxidase and generation of superoxide. Further, Akita/ACE2KO myocardium exhibited increased phosphorylation of Jak2, Stat3 and ERK1/2 signaling pathways, in addition to enhanced matrix metalloproteinase (MMP)-2 and MMP-9 activation. Endothelial-dependent vasodilation was markedly impaired in mesenteric resistance artery obtained from the ACE2/Akita double mutant mice.

CONCLUSIONS: Loss of ACE2 induced oxidative stress and modulation of pathological signaling in combination with endothelial dysfunction underlies impaired systolic function in diabetic cardiomyopathy. Enhancing ACE2 action may prevent the cardiovascular complications associated with diabetes.

SUPERVISOR: GAVIN Y. OUDIT

Antiviral therapy abrogates cholangitis in the NOD.c3c4 mouse model of primary biliary cirrhosis

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Introduction: A human betaretrovirus resembling the mouse mammary tumor virus (MMTV) has been characterized in patients with primary biliary cirrhosis (PBC) and MMTV infection is associated with aberrant pyruvate dehydrogenase complex (PDC)–E2 expression. The NOD.c3c4 mouse model of PBC also has evidence of MMTV infection in the liver and lymphoid system, and MMTV proteins have been located in diseased biliary epithelium and found in the same distribution as aberrant mitochondrial antigen expression. In addition, the production of anti-mitochondrial antibodies directly correlates with anti-MMTV production in the NOD.c3c4 mouse. In this study, we investigated the causal association of MMTV infection with PBC by treatment of the NOD c3.c4 mouse with anti-retroviral therapy.

Methods: Weanling female NODc3.c4 mice were treated with anti-retroviral therapy, neutralizing anti-MMTV antibodies and preliminary studies were attempted with AAV encoding shRNA to MMTV. Response to treatment was assessed by measuring MMTV transcripts in liver, alkaline phosphatase levels in serum and liver histology using a modified Ishak score.

Results: Anti-retroviral therapy regimens with reverse transcriptase inhibitors and protease inhibitors resulted in a significant reduction in serum alkaline phosphatase, abrogation of cholangitis and decreased MMTV levels in the liver. Improvements in hepatic histology and biochemistry were observed in NOD.c3c4 mice treated with lamivudine and zidovudine. However, the mice developed biochemical rebound, increased levels of hepatic MMTV RNA and variations in the MMTV pol gene consistent with viral resistance. Neutralizing anti-MMTV therapy also abrogated cholangitis with significant reduction in alkaline phosphatase. Preliminary AAV studies did not significantly impact on reduction of MMTV levels but improved histology.

Conclusions: The response to antiretroviral therapy suggests that retroviral infection plays a role in the development of cholangitis in this model. The NOD.c3c4 mouse can be used to test the hypothesis that MMTV triggers autoimmune biliary disease in mice.

Supervisor: Andrew Mason

IDENTIFICATION OF THE DUCK INTERLEUKIN-10 RECEPTOR-1 AND EXPRESSION ANALYSIS OF NOVEL INTERLEUKIN-10 ISOFORMS IN THE DUCK HEPATITIS B MODEL

Yao Q, Fischer KP, Tyrrell DL and Gutfreund KS

INTRODUCTION: Interleukin-10 (IL-10) has an important role in limiting pro-inflammatory responses and has been implicated in the pathogenesis of
IL-10 binds with high affinity to IL-10 receptor 1 (IL-10R1) and low affinity to IL-10R2. Furthermore, blockade of IL-10 signaling has been shown to restore antigen-specific T cell effector function in persistent viral infections. We have recently identified duck IL-10 (DuIL-10) and its isoform protein (DuIL-10Δexon5) that lacks one receptor binding site for IL-10R1. The ***aim*** of this study was to identify and characterize duck IL-10R1 (DuIL-10R1) and to explore the role of IL-10 signaling in duck hepatitis B virus (DHBV) infection.

METHODS: The open reading frame of DuIL-10R1 was obtained by RT-PCR with primers based on chicken sequence and 5' RACE and 3'RACE from duck splenocytes. DuIL-10, DuIL-10Δexon5 and IL-10R1 transcript levels were assessed by real-time PCR in PBMC's and tissue of DHBV-naïve animals and liver of ducks infected with DHBV.

RESULTS: The predicted DuIL-10R1 protein showed an identity of 63%, 28% and 27% with chicken, human and murine homologues, respectively. Transcripts of DuIL-10R1 and DuIL-10-isoform proteins were predominately expressed in primary and secondary immune organs and lung. DuIL-10R1 transcripts were down-regulated in PBMCs following mitogen stimulation and transcripts of DuIL-10 isoform proteins were differentially expressed in the liver of ducks with congenital or acute resolving DHBV infection and uninfected age-matched control animals.

CONCLUSIONS: DuIL-10R1 has significant homology with mammalian and chicken homologues. The interaction of DuIL-10R1 with the identified two DuIL-10 isoform proteins and their individual roles in duck immune responses and DHBV infection can now be further investigated.

SUPERVISOR: Klaus S. Gutfreund

CXCR7 protein is strongly expressed in preB- ALL but not T-ALL or AML cells

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INTRODUCTION. After the identification of CXCR7 as a second receptor for CXCL12/SDF-1 chemokine, verification of CXCL12/SDF -1-mediated processes in tumor and hematological malignancies gained more importance. Previously we reported that CXCR7 is indispensable for transendothelial migration of B- but not T-cell lines towards a CXCL12/SDF-1 gradient. Others reported that CXCR7 protein is not expressed on the surface of leukocytes and normal hematopoietic stem cells. The objective of this study was to determine whether CXCR7 is expressed in malignant blasts in acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) patients.

METHODS. Using immunohistochemistry (IHC) with anti-CXCR7 MoAb (clone 11G8, ChemoCentryx), we investigated the expression pattern of CXCR7 in tissue microarrays (TMAs) from paraffin embedded bone marrow (BM) biopsies from 81 ALL (70 preB-ALL and 11 T-ALL) and 145 AML patients. We also evaluated CXCR7 mRNA expression (by RT-PCR) in BM-mononuclear cells (BM-MNC) of preB-ALL, T-ALL, and AML patients and the expression of CXCR7 mRNA and protein (by flow cytometry) in leukemic lymphoid (B cell lines: Raji, NC-37, Ramos, Nalm6 and REH; T cell lines: Jurkat and CEM) and myeloid cell lines (KG-1, HL-60, THP-1, U-937, K562 and HEL).

RESULTS. In preB-ALL TMAs, CXCR7 was immunopositive in 57% (strongly-37%; weakly-20%) of the patients, in contrast to immunonegative IHC staining in 100% of T-ALL and 86% of AML. However, weak immunopositivity was observed in 14% of AML patients. CXCR7 mRNA was expressed strongly in preB-ALL compared to T-ALL and AML BM-MNC. CXCR7 mRNA was strongly expressed in B-cell lines (Raji, NC-37, Ramos and REH) but only weakly in T-cell lines. KG-1, HL-60, THP-1, and HEL expressed CXCR7 mRNA which was absent in U937 and K562 cell lines. Surface expression of CXCR7 protein was strongest in B cell lines (34 - 48%) and weakest in myeloid cell lines (0.23 - 11%).

This work was supported by CBS/CIHR grant to AJW.

HIV protease inhibitors downregulate expression of glutamate transporters and increase excitability of astrocytes

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Introduction: The efficient penetration of antiretroviral drugs into the central nervous system (CNS), which is correlated to greater reduction of HIV viral replication in cerebrospinal fluid, is paradoxically associated with poorer neurocognitive performance. The reduced expression and dysfunction of glutamate transporters has been associated with the development of HIV-associated dementia. Herein, we hypothesize that protease inhibitors with high CNS penetration exert neurotoxicity through their effects on glutamate transporters expressed on astrocytes.

Methods: Primary human astrocytes were exposed to various concentrations of amprenavir and lopinavir. Gene expression was measured by real time RT-PCR and protein expression of glutamate transporters was determined by Western blots. Astrocyte excitability was examined by measuring intracellular calcium flux [Ca_i^{2+}] in Fluo-8-loaded cells with or without the presence of glutamate (1.5 mM).

Results: Primary human astrocytes exposed to amprenavir or lopinavir showed a concentration-dependent reduction in transcript levels of excitatory amino acid transporter 2 (EAAT2), the primary glutamate transporter on astrocytes in cerebral cortex. Chronic exposure of amprenavir or lopinavir was also associated with the lower protein expression of EAAT2. In contrast, amprenavir and lopinavir did not alter gene expression of the glutamate transporter, EAAT1, and the neutral amino acid transporter, ASCT1, in primary human astrocytes. Acute application of lopinavir did not affect cytosolic calcium flux [Ca_i^{2+}] in primary human astrocytes while chronic exposure of lopinavir increased both spontaneous and glutamate-evoked transient rises in [Ca_i^{2+}], indicative of increased excitability.

Conclusions: Our results indicate HIV protease inhibitors, amprenavir or lopinavir, decrease expression of a glutamate transporter, which could disrupt astrocytes' ability to regulate glutamate levels in the brain leading to excitotoxicity and neurocognitive impairment.

Supervisor: Dr. Christopher Power

Isolation of the Human Betaretrovirus and Demonstration of Integration Sites in Patients with Primary Biliary Cirrhosis

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INTRODUCTION

A human betaretrovirus (HBRV) resembling the mouse mammary tumor virus has been cloned from biliary epithelium and lymph nodes of patients with primary biliary cirrhosis (PBC). The virus has been detected in 75% of perihepatic lymph nodes by RT-PCR and immunohistochemistry. The hypothesis that this agent is a human pathogen is highly controversial and others suggested that viral infection may be attributable to PCR contamination. Accordingly, we have introduced two PCR amplification-free assays, QuantiGene viewRNA and QuantiGene assay, as well as linker mediated PCR (LM-PCR) to detect HBRV and viral integration sites. Initially, capillary sequencing was used to identify integration sites from LM-PCR and then we have applied solexa deep sequencing to study the profiling of viral integration sites in clinical samples for a solid proof of viral infection.

METHODS

HBRV was isolated *in vitro* by co-culture of lymph node homogenates from PBC patients with Hs578T cells. DNA was extracted from biliary epithelium cells (BECs), perihepatic lymph nodes, liver tissue as well as the co-cultured HS578T cells. Integration sites were identified using LM-PCR with virus-specific and linker primer by capillary sequencing or illumina next generation sequencing. Genuine integration sites included the 3' end of the viral LTR, a human genomic sequence within 3 bases of the LTR junction and then the linker sequence. HBRV probes were employed for QG assay and viewRNA on Hs578t cells, BECs and liver tissue of patients with PBC and other liver diseases.

RESULTS

HBRV was detected by RT-PCR in 16 supernatants from 28 sub-cloned Hs578T co-cultured cells. HBRV particles were identified by electron microscopy and 19 unique integration sites were identified with capillary sequencing in infected Hs578T DNA but not in controls, and 789 unique integration sites were further acquired with solexa sequencing. Unique HBRV integration sites were identified in 2 out of 17 PBC liver samples vs. 0 out of 19 controls, and 7 out of 9 PBC BECs vs. 1 out of 14 controls. Notably, we have acquired 1853 unique sites from one of the PBC BECs with Solexa. In total, the majority of integration sites was found within genes or within 100kb of transcription start sites and clustering in sites was observed. QG and View RNA recapitulated the data from the integration site project where HBRV RNA was detected in 5 out of 6 PBC BECs. Of interest HBRV RNA was found in 2 BECs derived from patients with autoimmune hepatitis (AIH), a disease with cross over of symptoms and features with PBC. These two additional BECs have been collected for further verification with LM-PCR plus Solexa sequencing.

CONCLUSIONS

The viral isolation studies and the detection of viral integration sites in the human genome provide proof that patients with PBC have infection with a transmissible betaretrovirus. The detection of betaretrovirus within genes and in close proximity to transcription start sites suggests a hypothesis that integration may effect gene regulation in patients with PBC. QG and ViewRNA results confirmed the integration data, and further implied the possibility of association with AIH. Large scale case-control study on PBC vs. control liver disease with multiple assays suggest a promising method to monitor viral titer associate with pathogenesis of PBC and antiviral therapy.

SUPERVISOR

Andrew L. Mason

Young Adults with Inflammatory Bowel Disease have Higher Rates of Depression Irrespective of Age of Diagnosis

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BACKGROUND: Clinical depression is thought to occur frequently in adolescents with inflammatory bowel disease (IBD). Furthermore, an IBD diagnosis at a later age has been shown to be associated with increased depressive symptoms.

AIM: To determine if young adults (aged 18-30) have higher depression scores compared to healthy controls; and to determine whether those diagnosed with IBD before 18 years of age had different depression scores than those diagnosed in adulthood.

METHODS: IBD patients (aged 18-30y) were identified using a University-based gastroenterology patient care database. Patients were recruited in clinic, by mail, and by telephone. Age and gender matched healthy controls were recruited through advertisement in local newspapers. Participants were consented and completed the validated Beck Depression Inventory II (BDI-II) and demographic information sheets. IBD patients were assessed in two groups; those diagnosed before 18 yr of age and those diagnosed at age 18 yrs or older, and were compared to age- and gender-matched healthy controls. Higher scores on the BDI-II indicate more depressive symptoms.

RESULTS: 203 patients with IBD and 106 healthy controls completed the questionnaire. Eleven (4 IBD and 7 controls) were excluded because they did not complete the entire BDI-II. Table 1 shows the age and gender distribution as well as the BDI-II scores by age of diagnosis compared to healthy controls. The BDI-II scores were significantly higher (i.e. more depression) in patients with IBD compared to controls (p=0.006). Rates of depression (BDI-II score > 13) were significantly higher in IBD patients compared to controls (23.1% v. 10.1%, p=0.007). Overall, female participants had higher BDI-II scores than males, but this difference was not statistically different (7.8 ± 0.74 versus 8.4 ± 0.61, p=0.538). There was no difference in depression score when examined relative to age of diagnosis or type of IBD.

Table 1. Demographic and Beck Depression scores for IBD patients and healthy controls

	IBD - Dx<18	**IBD – Dx 18-30**	**Control**	**p-value**
N	95	104	99	-
% Female	51.6%	69.2%	63.3%	0.034
Age (years)*	22.8 ± 0.35	27.0 ± 0.32	24.0 ± 0.34	<0.0001
% Crohn's	52.8%	47.2%	-	0.084
BDI-II (all patients)*	9.2 ± 0.82	9.2 ± 0.80	6.1 ±0.76	0.006
BDI-II (females)*	9.8 ± 1.21	9.7 ± 1.06	5.9 ± 0.80	0.010
BDI-II (males)*	8.6 ± 1.14	8.28 ± 1.06	6.4 ± 1.56	0.426

* mean ± SE

The Developmental Milestone of Autonomy is Delayed when Inflammatory Bowel Disease is Diagnosed before the Age of 18

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BACKGROUND: Children with chronic illnesses diagnosed in childhood often achieve fewer milestones, or at a later age, than healthy children. Interestingly, the diagnosis of inflammatory bowel disease (IBD) earlier in childhood (age 8 to 11 yrs) appears to impact milestones to a lesser degree than if the diagnosis was made in adolescence.

AIM: To determine at what age in childhood the diagnosis of IBD maximally impacts developmental milestones and which unique milestones are most affected.

METHODS: IBD patients (18-30y) were identified using a University-based gastroenterology patient care database and recruited in clinic, by mail, and by telephone. Interested participants were consented and provided questionnaires to complete and return by mail. The questionnaires determined demographics and the previously validated Course of Life Questionnaire was used to assess timing of milestones in domains of autonomy, psychosexual development, social development, anti-social behavior, and substance use and gambling. The maximal score in each domain is listed in the table below; the higher the score the closer to "normal".

RESULTS: 203 patients with IBD completed the questionnaires. 60.6% were female and 63.5% had a diagnosis of Crohn's disease. Table 1 demonstrates the combined IBD Course of Life scores by age of diagnosis (Dx) and milestone domain. Results for Dx<12 and Dx12-17 were compared to Dx18-30. The diagnosis of IBD before age 12 and between age 12 and 17 negatively impacts the developmental milestone of autonomy but does not affect the other core milestones. Multivariate analysis demonstrated that those most affected by an IBD diagnosis during childhood are males and those diagnosed with Crohn's disease.

Table 1. Course of Life Scores by Age of Diagnosis

	Dx<12	**Dx 12 – 17**	**Dx 18-30**	**p-value**
N	28	69	106	-
Age (Mean ±SE)	22.4 ± 0.67	23.1 ± 0.41	27.0 ±0.32	<0.001
%CD	64.3	73.5	57.5	0.101
Milestone				
Autonomy (/12)	7.6 ± 0.24	7.9 ± 0.14	8.37 ± 0.08	0.001
Psychosexual (/8)	6.5 ± 0.31	6.5 ± 0.17	6.91 ± 0.10	0.105
Social (/24)	20.8 ± 0.52	20.6 ± 0.27	20.8 ± 0.21	0.818
Anti-social (/8)	4.8 ± 0.20	4.96 ± 0.14	4.79 ± 0.09	0.532
Substance-Use (/24)	14.1 ± 0.46	14.3 ± 0.29	14.7 ± 0.26	0.368

CONCLUSION: A diagnosis of IBD before the age of 18disease negatively impacts the developmental

Association between estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes: a longitudinal population-based study

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For the Alberta Kidney Disease Network.

Introduction: Most studies of chronic kidney disease (CKD) and outcomes focus on mortality and endstage renal disease (ESRD), with limited data on other adverse outcomes. This study examined the association between proteinuria, eGFR and adverse cardiovascular (CVD) events.

Methodology: Population-based longitudinal study with participants identified from a province-wide laboratory registry that includes eGFR and proteinuria measurements from Alberta, Canada, between 2002 and 2007.Of 1,526,437 subjects with at least 1 serum creatinine record; 920,985 (60.3%) and 102,701 (6.7%) had ≥1 dipstick proteinuria and ≥1 urine albumin-creatinine ratio (ACR) respectively. We considered time to hospitalization for 1 of 4 indications: (congestive cardiac failure [CHF], coronary bypass grafting [CABG] or percutaneous angioplasty [PCI], peripheral vascular disease [PVD] and stroke/transient ischaemic attacks [CVA]).

Results: During median follow-up of 35 (range 0-59) months), 1,891 (0.2%) of those with dipstick proteinuria hospitalized for PVD, 7,309 (0.8%) for PCI or CABG, 4,265 (0.5%) for CHF, and 4,692 (0.5%) for CVA/TIA. From the ACR cohort, 367 (0.4%), 2,218 (2.2%), 1,555 (1.5%), 1,157 (1.1%) had PVD, PCI/CABG, CHF and CVA/TIA respectively. In both cohorts, age-adjusted rates of CHF and CVA were increased ($p<0.001$) at lower levels of eGFR and with heavier proteinuria. While the risk of CABG/PCI and PVD increased ($p<0.0001$) with heavier proteinuria, there were fewer events in subjects with lower eGFR. In fully adjusted models, compared to subjects with eGFR of 45-59.mL/min/1.73m^2 and no proteinuria, subjects with heavy proteinuria by dipstick and eGFR of ≥60mL/min/1.73m^2 had higher rates of CABG/PCI and CVA; (1.4 [95% CI, 1.3-1.5]) vs (1.9 [95% CI, 1.6-2.3]) and 0.68 [95% CI, 0.62-0.74]) vs (1.43 [95% CI, 1.16-1.75]) respectively. Similar results were obtained in subjects with proteinuria measured by ACR.

Conclusions: Risks of major CVD events at a given level of eGFR increased with higher levels of proteinuria. The findings extend current data on risk of mortality and ESRD, and that proteinuria is of incremental prognostic benefits at every level of eGFR. These data support the use proteinuria with eGFR for definition and risk stratification in CKD.

Supervisor: Dr Marcello Tonelli

Diabetes is not an Adverse Prognostic Factor in Patients with Cardiac Disease Undergoing Non-Cardiac Surgery

Mikael Hanninen

ABSTRACT

INTRODUCTION: Whether surgical risk is modified by the presence of diabetes or diabetes therapies in patients with pre-existing heart disease (coronary disease (CAD) or heart failure (HF)) remains a matter of controversy.

METHODS: Retrospective cohort study linking 4 administrative databases in Alberta, Canada.

RESULTS: 32 834 patients with CAD or HF underwent non-cardiac surgery between 1999 and 2006 and 9305 (28%) had diabetes mellitus. All-cause 30-day mortality after non-cardiac surgery was 6.4% in patients with diabetes and 6.1% in those without diabetes (crude OR 1.05 [95% CI 0.95-1.16], multivariate-adjusted OR 0.97 [95% CI 0.87-1.08]). In the 24037 patients $\geq$65 years old, the unadjusted mortality was 7.5% in those with diabetes (5.7% in insulin-treated diabetes, 8.0% in non-insulin-treated diabetes) and 7.5% in individuals without diabetes. Multivariate analysis confirmed that diabetes was not associated with increased mortality (aOR 0.85 [95% CI 0.69-1.03] for any diabetes, aOR 0.88 [95% CI 0.69-1.11] for insulin-treated diabetes, and aOR 1.07 [95% CI 0.94-1.20] for non-insulin treated diabetes). None of the antidiabetic medications were associated with perioperative mortality, but preoperative use of ACEi/ARB (aOR 0.81, 95% CI 0.73-0.91), beta-blocker (aOR 0.82, 95% CI 0.72-0.93), or statin (aOR 0.65, 95% CI 0.55-0.78) were associated with lower mortality.

CONCLUSIONS: Neither diabetes nor exposure to any antidiabetic drugs preoperatively were associated with increased perioperative mortality in cardiac patients undergoing non-cardiac surgery. However, those not using ACEi/ARB, beta-blockers, or statins preoperatively exhibited higher mortality rates, emphasizing the importance of optimizing evidence-based therapy prior to elective surgery.

SUPERVISOR: Dr. Finlay McAlister, MD, FRCPC

Management of *Clostridium difficile* infection and the effect on mortality

Holly Hoang, Stephanie Smith

INTRODUCTION

Clostridium difficile infection (CDI) accounts for 15-25% of antibiotic-associated nosocomial diarrhea (1). Treatment guidelines have been developed to optimize the management of this common cause of hospital morbidity (2). The objective of this study was to examine local rates and risk factors for CDI-related mortality, and to assess the degree of adherence to treatment guidelines and the effect on mortality rates.

METHODS

All patients admitted to the University of Alberta Hospital, Edmonton who died between 2008-2010 with a stool sample positive for *Clostridium difficile* toxin within the preceding 1 month were identified. Baseline demographics and antibiotic exposure were collected to identify risk factors for CDI-acquisition. Factors including time to treatment, treating service, and adherence to the treatment guidelines were studied to determine their effect on mortality.

RESULTS

41 patients met the inclusion criteria of which 39 patients had complete charts available for review. 34/39 (87.2%) had documented antibiotic exposure prior to CDI-acquisition. 34/39 (87.2%) were treated for CDI. Of the 34 treated for CDI, 12 of the deaths were attributable to CDI.

Forty three percent of those treated > 2 days after symptom onset had a CDI-attributable death compared with only thirty percent of those treated ≤ 2 days from symptom onset although this was not statistically significant (p=0.487)

20/34 (58.8%) patients were treated according to the treatment guidelines. Although there was a trend towards increased CDI-attributable mortality in those not treated according to guidelines (50% vs 25%), this did not reach statistical significance (p=0.163).

CONCLUSIONS

Treatment of CDI according to guidelines occurred in only 20/34 (58.8%) of patients included this study. Those patients not treated according to guidelines had a trend towards higher rates of CDI-attributable mortality. This underscores the relevance of treatment guidelines in the management of CDI and highlights areas for improvement.

SUPERVISOR

Dr. Stephanie Smith, Infectious Diseases. University of Alberta, Edmonton.

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THE HOST RESTRICTION FACTOR TETHERIN MODULATES NEUROAIDS

Polyak M, Vivithanaporn P, Maingat F, Pearson K, Meeker R, Cohen E, Power C.

INTRODUCTION. The lentiviruses, human (HIV-1) and feline (FIV) immunodeficiency viruses, cause neurological disease, termed neuroAIDS. Variable neuroAIDS severity has been reported in individuals infected with different HIV-1 clades/subtypes. Interferon-responsive host restriction genes have been implicated in immune defense during HIV/AIDS; however, the role of these genes in neuroAIDS is unknown.

OBJECTIVE. Determine the contributions of host restriction factors to neuroAIDS.

METHODS. Host gene expression was measured in HIV-1 or FIV-infected and uninfected brains and cultured cells. Cats were infected with the neurovirulent FIV strain (FIV_{ch}) or another strain, FIV_{ncsu}, with subsequent neurobehavioral and molecular analyses.

RESULTS. *In vitro* studies showed that human microglia expressed high levels of all restriction factors including the prototypic host restriction factor, Tetherin, which also showed increased expression in HIV+ brains. Tetherin was up-regulated with FIV infection of feline primary peripheral blood mononuclear cells. *In vitro,* Tetherin induction was FIV+ strain-dependent (FIV_{ncsu}) in myeloid cells, which accompanied reduced neuronal injury. *In vivo* FIV_{ch} and FIV_{ncsu} infections resulted in similar levels of immunosuppression (blood $CD4^+$ T cell depletion) and viral burden (plasma and brain). However, neuroinflammatory genes (*CD3*ε*, TNF*α) were increased in FIV_{ch} brains, but not in FIV_{ncsu}. Conversely, FIV_{ncsu} infection induced interferon-responsive genes (*IRF3, MxA, Tetherin*) in the brain with reduced neurological impairment ($p<0.05$).

CONCLUSIONS. Lentivirus infections induce Tetherin expression in neural macrophages and microglia in a viral strain-dependent manner, which limits ensuing neurovirulence.

SUPERVISOR. Dr. Christopher Power.

Postal Survey of Pregnancy in Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients

Teo, M and Keeling, S.

Objective: Pregnancy in women with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) is heterogenous, with variable effects of disease on pregnancy and pregnancy on disease. Pre-conception counseling will help limit disease flares, avoid medication-related teratogenicity and help towards a healthy pregnancy. The objective of this study was to describe the impact of RA and SLE on pregnancy and whether it affected future pregnancies.

Methods: A group of female RA and SLE patients under the age of 70 were identified during a chart review for another study of nine academic rheumatologists. A self-report questionnaire was created to review all pregnancies (including miscarriages and terminations) in SLE and RA patients and quantify disease activity and medication use during pregnancy. The questionnaire was mailed to 180 RA and 40 SLE patients with a postage-paid return envelope.

Results: Of 220 mailed questionnaires (180 RA, 40 SLE patients), 56 (31%) RA and 12 (30%) SLE patients returned completed questionnaires. Forty-nine (88%) RA and 10 (83%) SLE patients had been pregnant, where 18 (32%) RA and 4 (33%) SLE patients developed their disease prior to their first pregnancy. The number of miscarriages in RA and SLE patients during the first, second and third trimesters respectively was: 14 (25%), 2 (4%),0 and 4 (14%), 3 (10%) and 0. Twelve (25%) RA and 1 (10%) SLE patients reported active disease during pregnancy. Eleven (92%) RA patients continued DMARD therapy, including 1 (9%) on methotrexate, 2 (18%) on sulfasalazine, 5 (45%) on anti-malarials, and 6 (55%) took prednisone during their pregnancy. The SLE patient did not continue her medications nor took prednisone during her pregnancy. Four (23%) RA patients decided to not pursue further pregnancies as a result of increased disease activity during pregnancy and/or postpartum. One SLE patient aborted her last pregnancy because of increased past disease activity, 1 SLE patient had a tubal ligation and 1 SLE patient started using the oral contraceptive pill. Five (9%) RA and 1 (8%) SLE patient reported difficulties with becoming pregnant.

Conclusions: In this descriptive study, many RA and SLE patients had pregnancies predating their disease onset. SLE patients appeared more reluctant to continue therapy compared with RA patients. Despite literature supporting improved RA disease activity in pregnancy, half of the pregnant RA patients reported continued activity during pregnancy. The impact of SLE or RA disease activity on future pregnancies could not be reliably assessed due to low numbers. Comprehensive preconception discussions and close monitoring peripartum are required.

Evaluating Cardiac Risk in Inflammatory Arthritis Patients

Teo M, Hartmann D and Keeling S.

Objectives: Rheumatoid arthritis and associated inflammatory arthritides are independent risk factors for cardiovascular disease (CVD). While it is unclear how to manage these patients, cardiovascular risk stratification using existing scoring tools developed by cardiology is a starting point in evaluating cardiovascular risk. Study objectives included: (1) To evaluate the inflammatory arthritis patients in a university rheumatology practice and determine their cardiovascular risk according to existing risk stratification scores. (2) To determine if cardiovascular risk stratification occurs in a typical academic rheumatologist's practice.

Methods: A retrospective chart review of 440 inflammatory arthritis patients attending the practices of nine rheumatologists at the University of Alberta Hospital was performed. A pre-specified case report form detailing patient demographics, traditional cardiac risk factors and variables for the Framingham 2008 and Reynold's risk scores was used. Details of their arthritis, including seropositivity and medication use were collected.

Results: In this group of 440 patients (M:F = 117:323), 156 (35.5%) were CCP positive and 257 (58.4%) were RF positive. Complete Framingham risk scores were calculable for 3 (0.68%) patients, while the Reynold's risk score was calculable for none of the patients. Common cardiac risk variables not recorded by a rheumatologist included (1) positive family history of MI 440 (100%) patients, (2) diabetes 421 (95.7%) patients, (3) lipids status 322 (73.2%) patients and (4) smoking status 275 (62.5%) patients. When documented, patients were noted to be on the following medications: ASA 34 (7.7%) patients, anti-hypertensives 80 (18.2%) patients and lipid lowering medications 41 (9.3%) patients. Medication use for traditional cardiac risks was not documented in the chart for the following: ASA 127 (28.9%) patients, anti-hypertensives 123 (28.0%) patients and lipid lowering medications 130 (29.5%) patients. From the available data, the average Framingham risk of having a general cardiovascular event in 10 years was 29.7% (3 patients). Cardiovascular events were recorded in 2 (0.45%) patients. Rheumatologists ordered cardiac evaluation for 10 (2.3%) patients.

Conclusions: While cardiovascular risk reduction is a recognized goal in the inflammatory arthritis patient, this has not translated well into clinical practice after reviewing nine different rheumatologists. Even though cardiovascular risk stratification does not take into account the contribution of inflammatory arthritis to CVD risk, it is an important starting point from where further studies can identify inflammatory arthritis specific algorithms for reduction of CVD risk.

Association of Hub and Spoke Practice Patterns with Coronary Interventions and Outcomes in Non ST Evaluation Acute Coronary Syndromes (NSTE ACS): Insights from the Early Glycoprotein llb/llla Inhibition in NSTE ACS (Early ACS) trial.

Olga Toleva, Cynthia M. Westerhout, Paul W. Armstrong, Manohara Senaratne, Christoph Bode, Magnus Lindros, Diego Ardissino, Vitaly A. Sulimov, Gilles Montalescot

BACKGROUND: An early invasive strategy (i.e., <48h) is recommended in high-risk ACS pts, but the optimal timing is controversial. Because admissions to non-PCI hospitals (spokes) may cause delay, we evaluated PCI facility (hub)/spoke practice patterns and their association with outcomes in a large NSTE ACS trial in which patients were expected to undergo an invasive strategy.
METHODS: We compared hub and spoke differences in 9225 pts who had an early invasive strategy in EARLY ACS.
RESULTS: Hub pts more often had prior MI, PCI, or coronary artery bypass grafting (CABG), and higher TIMI risk scores (Table). Although spoke pts presented sooner, they had longer time to angiography: 37.8% >48h vs. 32.9% at hubs (p<0.001). High-risk pts - especially at hubs - had even greater delay to angio. Time from symptom onset to CABG was 61.8h longer for spoke pts; hospital stay was 1d longer. Ischemic outcomes were similar, but hub pts had more bleeding and transfusions.
CONCLUSIONS: Timely angiography and revascularization were often not achieved, especially in spoke sites. Better alignment between risk and use of early intervention is warranted. The basis for higher adjusted bleeding and transfusion rates in hub pts deserves further investigation.

Selected patient characteristics	**Hub n = 7455**	**Spoke N=1770**	**p**
Age (y)*	67.2 (61.4-75.1)	68.6 (59.8-75.0)	0.001
Previous MI/PCI/CABG rates, %	28.6 / 25.9 / 14.7	23.6 / 19.8 / 9.1	<0.001 (all)
Medical management/PCI/CABG after angiogram, %	28.9 / 59.5 / 12.4	27.4 / 61.2 / 12.0	>0.15 (all)
Time from symptom onset to angio (h)*	33.0 (26.1-45.9)	37.8 (28.7-57.5)	<0.001
High-risk TIMI score ≥5, %	36.1	32.4	0.004
High-risk TIMI with angio time >48h, %	37.9	29.0	0.001
High-risk TIMI with PCI time >48h, %	38.2	33.8	<0.001
Time from symptom onset to CABG (h)*	113.7 (70.7, 179.9)	175.4 (95.0, 282.8)	<0.001
Length of stay (d)*	4 (3, 7)	5 (4, 9)	<0.001
96-hr death/MI/recurrent ischemia/thrombotic bailout, %	9.8	9.3	0.559
Propensity-adjusted OR (95% CI)	1.08 (0.90-1.29)		0.415
30-day death/MI, %	11.7	11.5	0.800
Propensity-adjusted OR (95% CI)	1.04 (0.88-1.23)		0.631
120-h GUSTO severe/moderate bleeding, %	6.7	4.4	<0.001
Propensity-adjusted OR (95% CI)	1.56 (1.21-2.01)		<0.001
120-h RBC transfusions, %	8.2	4.9	<0.001
Propensity-adjusted OR (95% CI) for Hub vs. Spoke	1.55 (1.21-1.98)		<0.001

*Median (interquartile range).

Validation of an Automated Perfusion-Diffusion Lesion Assessment Tool

Trevor A Steve MD; Negar Asdaghi MD, FRCPC; Thomas Jeerakathil MD, MSc, FRCPC; Michael E Knash MD; Bilal Hameed MD; Christian Beaulieu, PhD, Ashfaq Shuaib MD, FRCPC; Derek Emery, MD, MSc, FRCPC; Kenneth S Butcher MD, PHD, FRCPC

INTRODUCTION: Perfusion (PWI) and diffusion-weighted (DWI) volume assessments in the clinical setting are generally qualitative. Although qualitative assessments have been shown to be inaccurate, quantitative volume measurements are time intensive and impractical in the emergent setting. Rapid and accurate assessment tools are therefore required. We aimed to validate an automated PWI-DWI assessment tool.

METHODS: The Perfscape (Olea Medical) software package was used to calculate Tmax+4s deficit, DWI lesion and penumbral (Tmax+4s-DWI) volumes automatically in ischemic stroke patients. PWI and DWI volumes were indpendently measured using manual planimetric techniques. Correlation and Bland-Altman analyses were conducted.

RESULTS: Seventy-six patients were assessed. The median time from onset to MRI was 9.48 hours (IQR= 5.81,17.43). Automated DWI volumes (17.3±41.0 mL) were strongly correlated with those measured manually (29.1±57.9 mL; Rho=0.929, $p<0.05$). Automated volumes were generally smaller than manual measurements (mean difference -11.8 mL, 95% limits of agreement (LA) -51.6, 28.0 mL). Similarly, automated (31.7±42.8 mL) and manual Tmax+4s perfusion deficit (52.6±68.2 mL) volumes were strongly correlated (Rho=0.908, $p<0.05$). Automated Tmax+4s PWI deficit volumes were generally smaller than manual measurements (mean difference -20.9, 95% LA -88.7, 46.9 mL). Mismatch ratios assessed automatically (7.0±17.1) were highly correlated with those derived from manually calculated volumes (6.88±22.6); (Rho=0.755, $p<0.05$). The automated software detected the presence of a mismatch ratio of >2.0 with sensitivity of 92.3% and specificity of 84%.

CONCLUSIONS: Automated DWI lesion and PWI deficit volume assessment is feasible. Automated software may facilitate treatment decisions based on penumbral imaging patterns.

SUPERVISOR: Dr. Ken Butcher

Table 1: Patient Characteristics.

Number of Patients	76
Median age	68.3
Age range	32-94
Male (%)	61.8
Median (IQR) time to MRI	9.5 (5.8-17.4)

Table 2: Automated and Manual MRI Volume Differences and Correlations.

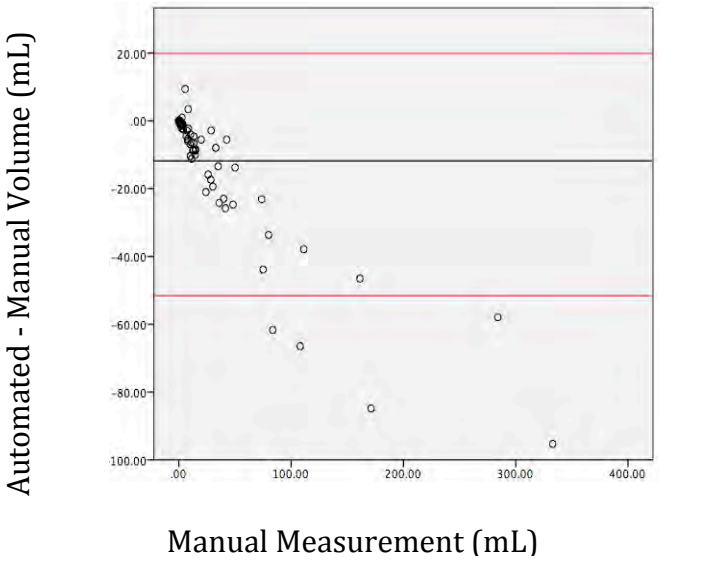
Parameter	Mean Automated Volume ± SD	Mean Manual Volume ± SD	Rank Sum Test	Spearman's Rho
Diffusion Lesion Volume (mL)	17.3 ± 41.0	29.1 ± 57.9	P < 0.0001	0.93
Perfusion Deficit Volume (mL)	31.7 ± 42.8	52.6 ± 68.2	P < 0.0001	0.91
Mismatch Volume (mL)	14.3±26.4	23.5±51.3	P = 0.195	0.63
Mismatch Ratio	7.0±17.1	6.88±22.6	P = 0.086	0.76

Table 3: Accuracy of automated mismatch ratio assessments.

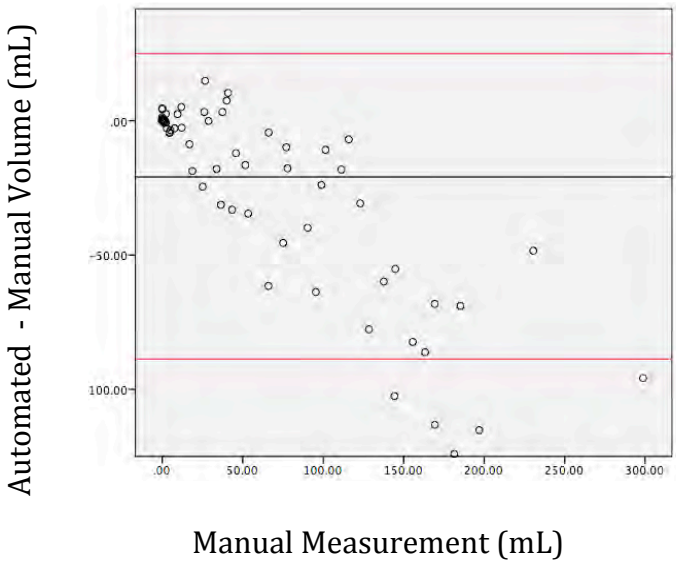
Mismatch Ratio	Sensitivity (%)	Specificity (%)
≥ 1.2	81.6	78.9
≥ 2.0	92.3	84.0

Figure 2: Bland-Altman plots of diffusion, perfusion and mismatch volumes/ratios measured manually and automatically. Mean differences are indicated by the solid line and the 95% limits of agreement are indicated by dashed lines.

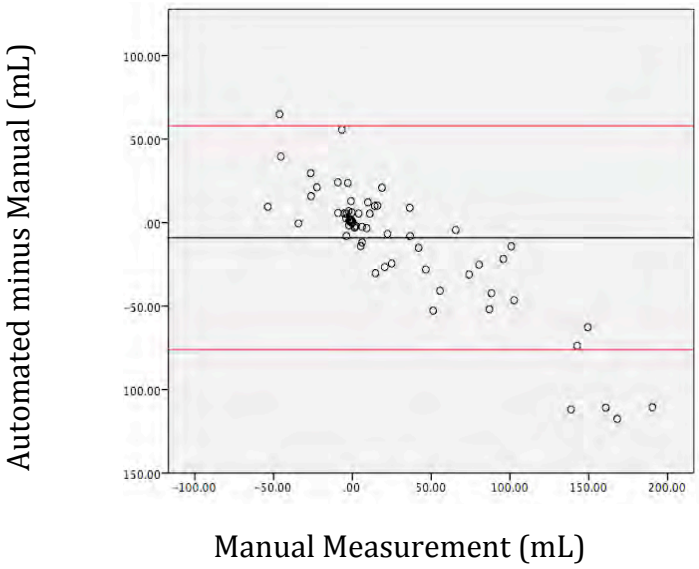
Diffusion Weighted Image Lesion Volume



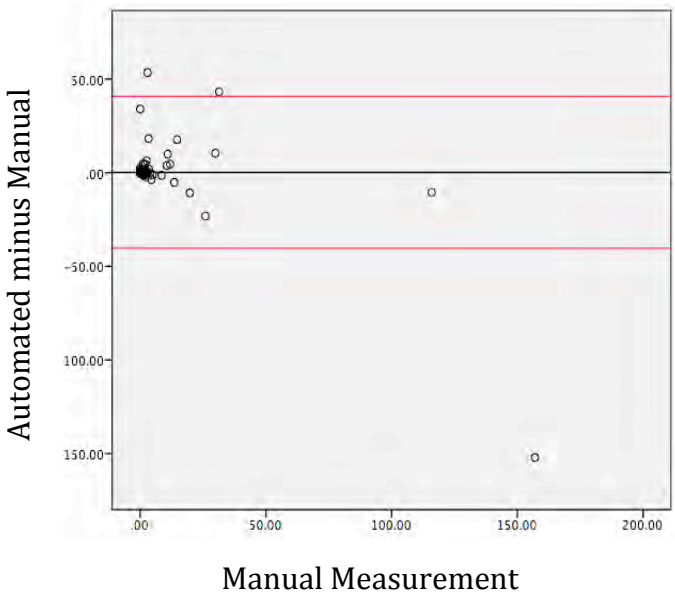
Perfusion Weighted Image Lesion Volume



Mismatch Volume



Mismatch Ratio



NIHSS Thresholds for Prediction of Perfusion Deficits in Acute Cerebrovascular Syndromes

Trevor A Steve MD; Michael E Knash MD; Negar Asdaghi MD, FRCPC; Thomas Jeerakathil MD, MSc, FRCPC; Ashfaq Shuaib MD, FRCPC; Derek Emery MD, MSc, FRCPC; Christian Beaulieu PhD, Kenneth S Butcher MD, PhD, FRCPC

INTRODUCTION: Perfusion-weighted imaging (PWI) in acute ischemic stroke patients provides useful diagnostic and prognostic information. The severity of clinical deficits is often part of the decision making process in selecting patients for PWI. We aimed to identify a threshold for clinical severity, based on the National Institutes of Health Stroke Scale (NIHSS) score, that would predict perfusion deficits as well as PWI-diffusion-weighted imaging (DWI) mismatch in patients presenting with acute focal neurological symptoms.

METHODS: Patients with acute ischemic cerebrovascular syndromes were imaged with PWI-DWI acutely and an NIHSS score was assessed prior to MRI. Manual planimetric measurements of Tmax+4s and DWI lesion volume were made. Patients were considered to have significant PWI deficits if the Tmax+4s volume was >10 ml. A PWI-DWI mismatch was considered to be $Tmax+4s_{vol}/DWI_{vol}>1.2$. We conducted an ROC analysis of the sensitivity and specificity of the NIHSS for prediction of PWI deficits and mismatch patterns.

RESULTS: A total of 76 patients were included. Logistic regression indicated that NIHSS score was a significant predictor of perfusion deficits (OR=1.4 per 1 NIHSS point, $p<0.001$). ROC analyses indicated good to moderate sensitivity and specificity of NIHSS score as a predictor of PWI deficits (AUC=0.86) and mismatch (AUC=0.68). An NIHSS ≥10 had a PPV and specificity for PWI deficits of 92.6% and 93.9% respectively but only 58.1% sensitivity. In our study, an NIHSS cutpoint of >=1 would have been required to capture all patients with significant PWI deficits.

CONCLUSIONS: Higher NIHSS scores do predict the presence of focal hypoperfusion, but even patients with mild clinical deficits often have blood flow changes. Penumbral imaging should be considered in all patients with neurological deficits, even when NIHSS scores suggest a mild clinical syndrome

SUPERVISOR: Dr. Ken Butcher

Table 1: Patient Characteristics

Variable	Patients with PWI Deficits	Patients without PWI Deficits
Number of Subjects (%)	43 (56.6)	33 (43.4)
Median (IQR) NIHSS	13.0 (7.0-18.0)	4.0 (3.0-5.5)
Average (Range) NIHSS	12.2 (1-23)	4.5 (0-18)
Median (IQR) time to MRI, hrs	7.5 (4.0-15.5)	13.0 (6.5-19.7)

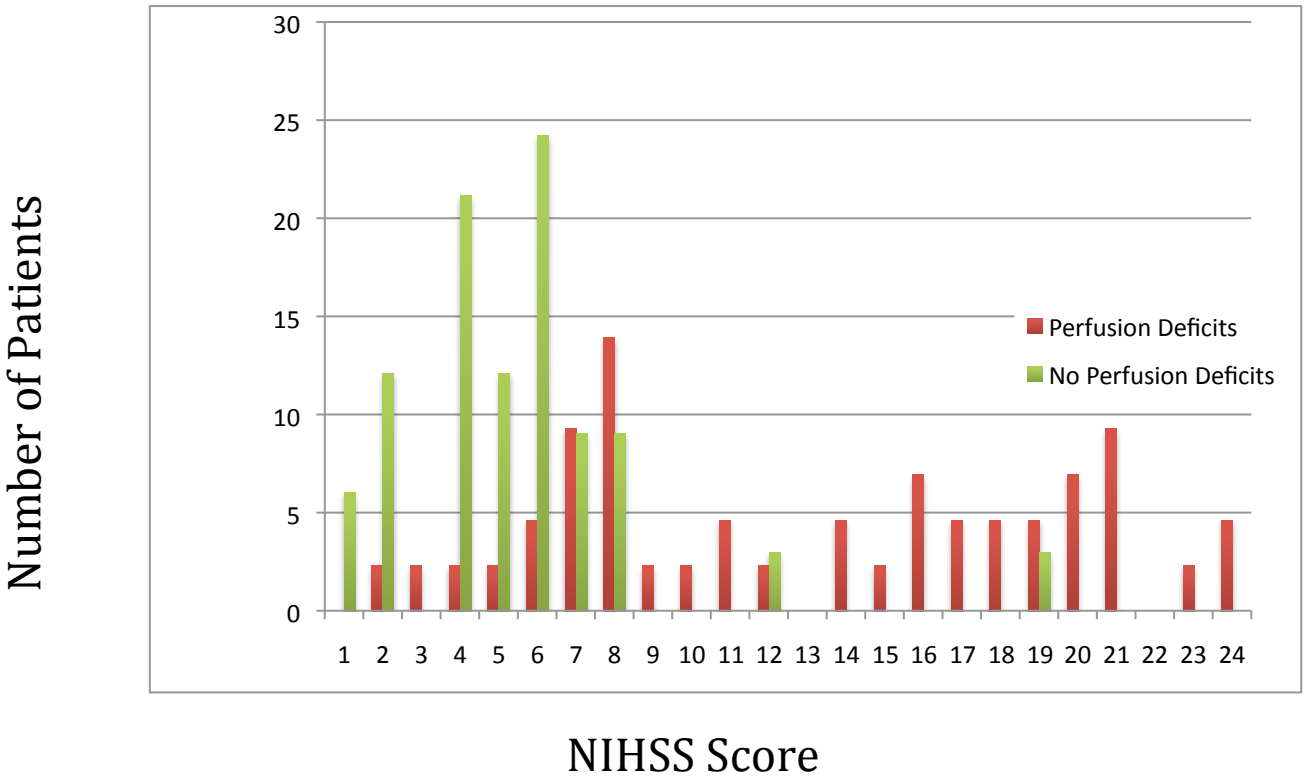
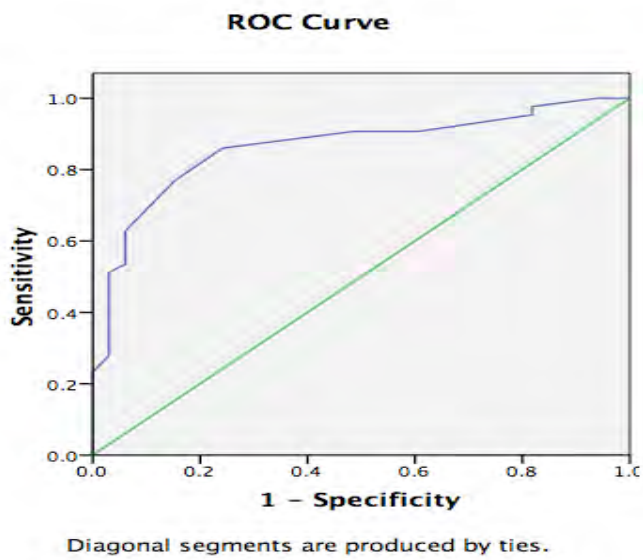
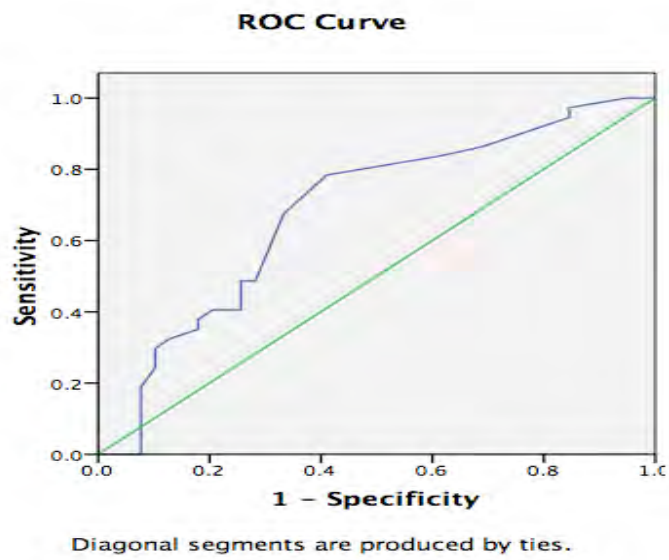


Figure 1
A histogram depicting the distribution of NIHSS scores for subjects found to have perfusion deficits and those in whom no perfusion deficits were identified.



A)



B)

Figure 2

A) Receiver operating characteristic analysis is shown for use of NIHSS score thresholds to predict perfusion deficits. The Area Under the Curve was 0.86.

B) Receiver operating characteristic analysis is shown for use of NIHSS score thresholds to prediction perfusion-diffusion mismatch. The Area Under the Curve was 0.68.

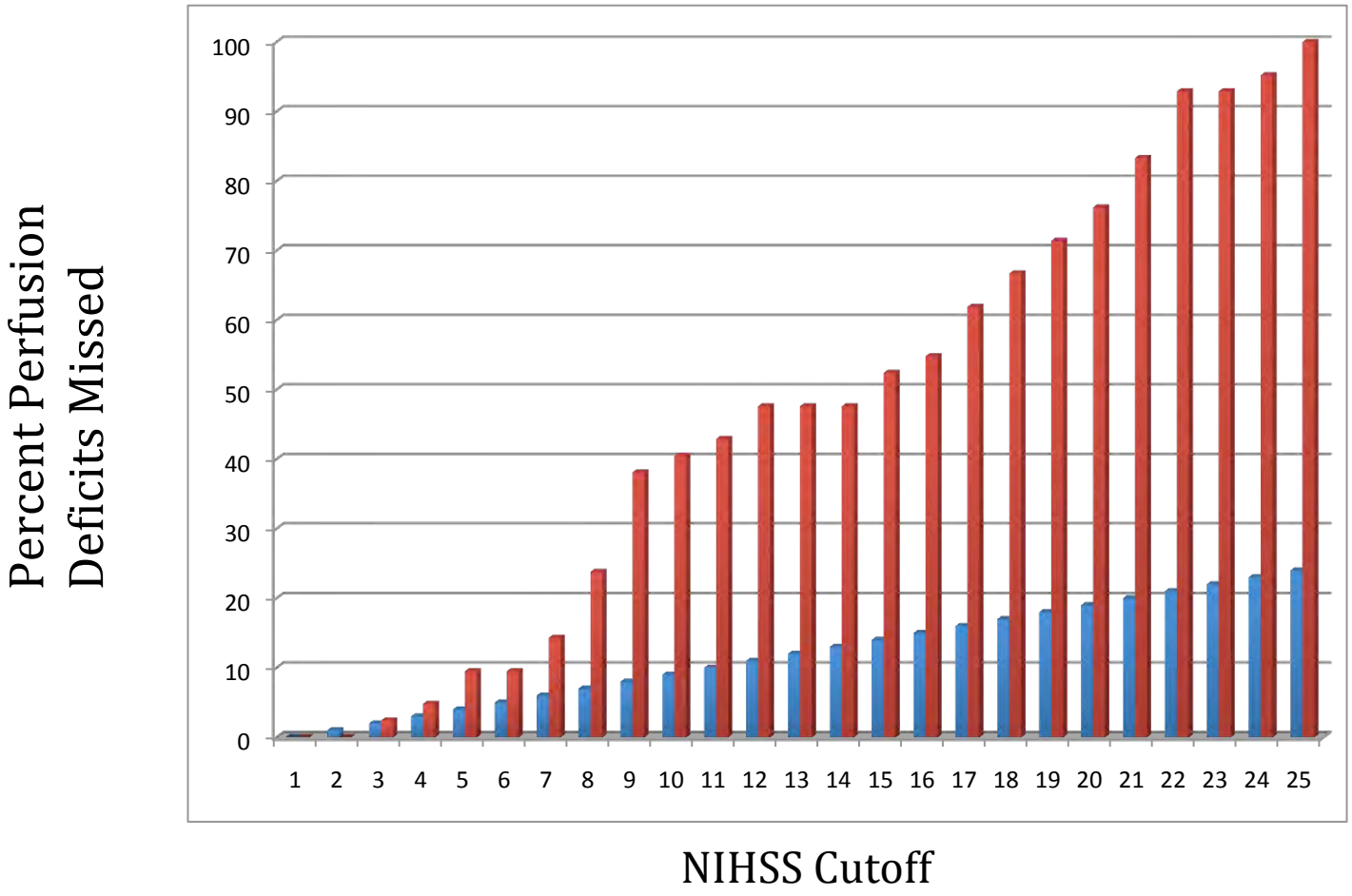


Figure 3
This figure graphs the percentage of subjects with perfusion deficits that would remain undetected if an NIHSS score threshold were applied to select subjects for perfusion imaging.

Quality Review of Therapeutic Hypothermia in the Coronary Care Unit of the Mazankowski Alberta Heart Institute

Khandekar, S and Tymchak, W

INTRODUCTION

Therapeutic hypothermia (TH) is indicated to preserve neurological function after cardiac arrest. A protocol for TH has been in use in the coronary care unit (CCU) since 2004. This quality review aimed to quantify short-term outcomes, as well as explore potential areas of improvement for the current CCU protocol.

METHODS

CCU admission records over a period from March 5, 2008 to March 4, 2010 were reviewed to identify patients admitted with ventricular tachycardia (VT) or ventricular fibrillation (VF) arrests. Information reviewed included circumstances of arrest, whether or not TH was used, time to return of spontaneous circulation (ROSC), time to target temperature, neurological function on discharge, and disposition. A survey was given to cardiologists, cardiology senior residents, and CCU nurses regarding perceptions and concerns about the current protocol.

RESULTS

Fifty-seven charts were reviewed, and 31 patients underwent TH. Average time before ROSC in TH patients was 30 minutes (2-60), compared with 21.1 minutes (1-120) in non- TH patients. Average time to target temperature was 7.5 hours. Twenty-seven patients (87%) had an infection following TH, 18 (66.7%) had aspiration pneumonia. Nineteen (61%) patients were noted to have some neurological decline after TH. Fourteen (45%) TH patients were discharged home, twelve (38.7%) died, and the remainder (16%) went to subacute, palliative, or long-term care facilities.

Forty-six surveys were completed (34.8% cardiologists, 23.9% senior residents, and 41.9% CCU nurses). Over 90% of respondents believed TH to be effective, and 58.7% had questions or concerns about the current protocol. Issues included perceived inappropriate use of TH, difficulties initiating TH outside of CCU, lack of formal neurological assessment prior to TH, and uncertainty regarding neuromuscular blockade.

CONCLUSIONS

Although this was a small number of patients, the results are comparable with what is shown in the literature, even with longer time to target temperature. Education and clarification regarding issues raised in this review can further improve the quality of patient care and patient outcomes following cardiac arrest.

SUPERVISOR

W Tymchak, MD

PREOPERATIVE USE OF THIENOPYRIDINES AND OUTCOMES AFTER SURGERY: A SYSTEMATIC REVIEW

Anita Au, MD[1]

Finlay A. McAlister, MD MSc[1,2]

ABSTRACT

Objective: To examine the outcomes associated with preoperative thienopyridine exposure.

Background: While studies have demonstrated excess risk of ischemic events if aspirin is withheld preoperatively, it is unclear whether thienopyridines should be stopped preoperatively.

Methods: Systematic review of studies comparing postoperative outcomes in patients who were versus were not exposed to thienopyridine in the 5 days prior to surgery.

Results: Of the 37 studies we included, 31 were in cardiac surgery and 6 in non-cardiac surgery (97% of outcomes were from the cardiac surgery studies); 3 studies were randomized, 34 were observational. Exposure to thienopyridine in the 5 days preceding surgery (compared to no exposure) was not associated with any reduction in postoperative MI (23 studies, 12 872 patients, 3.4% versus 3.0%, OR 0.98, 95% CI 0.72-1.34) but was associated with increased risks of stroke (16 studies, 10 265 patients, 1.9% versus 1.4%, OR 1.54, 95% 1.08-2.20), reoperation for bleeding (32 studies, 19 423 patients, 4.3% versus 1.8%, OR 2.62, 95% 1.96-3.49), and all-cause mortality (28 studies, 22 990 patients, 3.7% versus 2.6%, OR 1.38, 95% CI 1.13-1.69).

Results were identical when analyses were restricted to long-term users of thienopyridines who continued versus held the medication in the 5 days before surgery.

Conclusion: The use of a thienopyridine in the 5 days prior to surgery was not associated with any reduction in postoperative MI but was associated with higher rates of stroke, reoperation, and all-cause mortality. These data strongly support current ACC/AHA recommendations to withhold thienopyridines 5 days before surgery.

The Spectrum of Clinical Presentations in Autoimmune Pancreatitis: A Medical Chameleon?

Angeli Chopra MBBS, Aldo J. Montano-Loza MD, and Gurpal Sandha MBBS, FRCPC

Introduction

Autoimmune pancreatitis (also known as IgG4 disease) belongs to a spectrum of sclerosing diseases of unique histological and clinical characteristics. We present a spectrum of distinct presentations of this increasingly recognized autoimmune disease.

Methods

The medical records of 7 patients, labelled with a diagnosis of autoimmune pancreatitis, were retrospectively reviewed. Their clinical and biochemical presentation, IgG4 level, imaging characteristics and response to therapy (steroids with or without endoscopic stent placement) was analysed.

Results

Between 2006 and 2010, 7 patients (5 males) with a mean age of 59±15 yrs (range 30-72 yrs) were reviewed. Presenting symptoms included jaundice (6/7 pts), significant weight loss (3/7 pts), abdominal pain (2/7 pts) and malabsorption (1/7 pt). Cholestatic liver enzyme elevation was seen in 6/7 pts. Mean alkaline phosphatase was 673 ± 472 U/L (range 87-1600 U/L) and a mean bilirubin of 110±58 µmol/L (range 9-180 µmol/L). Mean lipase level was 209±229 U/L (range 12-635 U/L) and only 1 pt had a persistently elevated serum lipase. The IgG4 level was elevated in only 3/7 pts, and mean level was 0.90±0.92 g/L (range 0.10-2.66 g/L), and total IgG was normal in all pts (12±3 g/L, range 8-16 g/L). Diffuse enlargement of the pancreas was seen on abdominal imaging in 6/7 pts. ERCP documented a bile duct stricture in 5/7 pts and EUS revealed a pancreatic duct stricture in 1 pt. One pt underwent a Whipple's operation for presumed pancreatic cancer but was found to have autoimmune pancreatitis on surgical histology. Three pts had histological diagnosis. Six of the 7 pts received treatment with steroids and the 5 pts with biliary strictures (located in the common bile duct, 1 proximal, 4 distal) and had stent placement. After a mean duration of 23±17 months (range 3-53 months), 3 pts had successful removal of the stent with clinical and biochemical resolution off steroid therapy.

Conclusions

Autoimmune pancreatitis can present with pancreaticobiliary strictures and may mimic pancreatic cancer. The serum IgG4 level may not always be diagnostic and a high index of suspicion is required. Immune-suppressive therapy with or without endoscopic stenting remains the mainstay of treatment although the duration of treatment may need to be prolonged in select cases.

MAJORITY OF PATIENTS ON MAINTENANCE INFLIXIMAB ARE LATE FOR REGULARLY SCHEDULED INFUSIONS, A RETROSPECTIVE COHORT STUDY

Grenvil Gracias[1], Chad Evaschesen[2], Pam Osatiuk[3] and Richard N Fedorak[2]. 1 Faculty of Medicine, University of Alberta, AB. 2 Division of Gastroenterology, University of Alberta, AB. 3 BioAdvance Inc, Edmonton, AB.

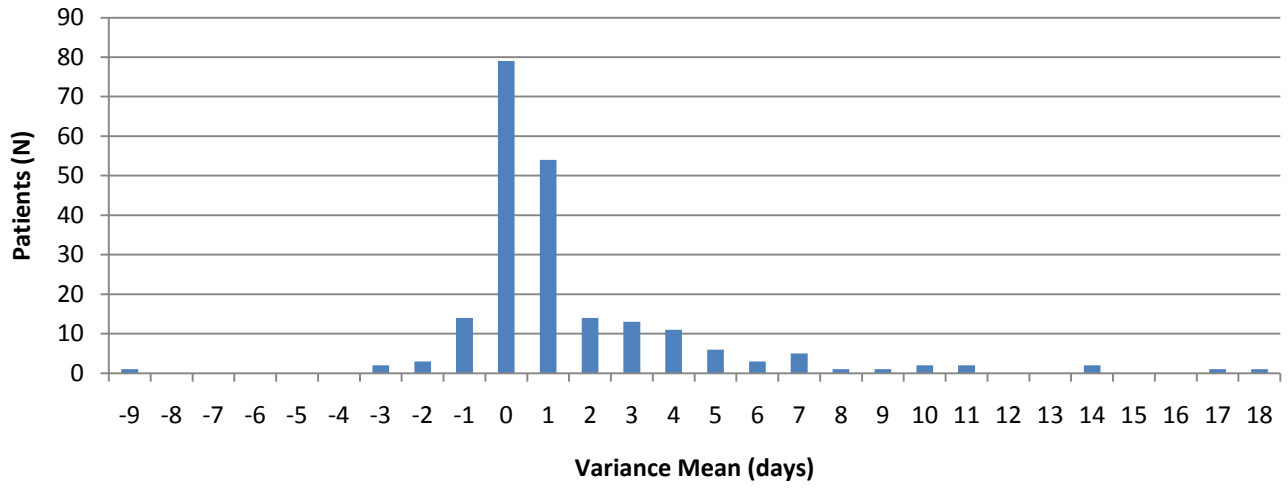
INTRODUCTION: Infliximab (IFX), a medication administered by intravenous infusion, has proven efficacy in inflammatory bowel disease (IBD) in both induction and maintenance of remission when using regularly scheduled infusion regimens. Subsequently, it has been shown that an episodic treatment regimen results in higher rates of IFX antibody formation, infusion reactions, and decreased clinical response. Non-adherence to a regularly scheduled infusion regimen would eventually lead to episodic therapy. The objective of this study is to determine patient adherence to regularly scheduled infliximab dosing and to characterize the non-adherent population receiving infliximab infusions with regard to demographics and clinical data.

METHODS: A random selection of 215 adult (age >17 yr) patients with Crohn's disease (CD) or ulcerative colitis (UC) on regularly scheduled infliximab had their infusion records reviewed from August 2008 to August 2010. Non-adherence was defined as not receiving the infusion on the scheduled date. Number of non-adherent infusions, average number of infusions, variance from the actual date of infusion to the scheduled infusion, and the total number of infusions received over the study period were recorded.

RESULTS: A summary of the results is presented below.

Patients N	Age Mean (Median) years	Gender M:F %	CD:UC%	Total Lifetime IFX infusions Mean (range)	Total IFX infusions over study period Mean (range)	Total Adherent IFX infusions over study period Mean (range)	% of IFX infusions adherent to scheduled time for study group	Variance from an individual IFX infusion in days Mean (range)	Cumulative number of days from scheduled IFX infusions Mean (range)	Number of weeks until a dropped IFX infusion Mean (range)
215	40.3 (40.0)	56:44	80:20	16.4+/- 9.8 (5-67)	10.46 (4-18)	4.26 (1-16)	40.7	3.24+/- 3.34 (0-26.0)	34.75 (0-260)	472 (23.7-4480)

Figure 1: Variance from an individual IFX infusion Mean



Over the 2 year interval of study only 3/215 (1.4%) patients were adherent to all IFX infusions. On average, patients received a total of 10.46 IFX infusions over the two year interval, however, only 4.26/10.46 (40.7%) of the infusions were adherent to the scheduled infusion time. The mean variance from an individual IFX infusion was 3.24 +/- 3.34 days (range 0 to 26 days). 37/215 (17.2%) patients were late four days or more per scheduled infusion. On average it would take 472 weeks for a patient to miss a dose of infliximab due to variance (range 23.7 to 4480).

CONCLUSIONS: A large majority (98.6%) of patients in this study were non-adherent to at least one of their regularly scheduled IFX infusions during the two year study period. Patients had an average variance of 3.24 days per regularly scheduled IFX infusion. 17.2% of patients were late 4 days or more which would result in a dropped dose of IFX after 25 months.

QUALITY ASSURANCE IN POST-GRADUATE MEDICAL EDUCATION: IMPLICATONS FOR RESIDENCY TRAINING PROGRAMS

Day, Isaiah; Lin, Andrew N. Division of Dermatology and Cutaneous Sciences, University of Alberta

INTRODUCTION: In the past few years quality assurance (QA) has become an increasingly important part of medical education for both Canadian and American training programs. Since this emphasis on quality assurance in residency programs is recent, most faculty members involved in teaching residents in dermatology training programs would not themselves have had experience with quality assurance. As a result, satisfying this requirement may be a challenge.

METHODS: In this presentation, we review published reports in which various residency training programs have satisfied this requirement. We searched the English language literature, using keywords “residency, training, project, quality, assurance, improvement, medical errors, and safety” for papers published after Jan 1990.

RESULTS: We found 14 articles that provide detailed descriptions of QA curricula in family practice, internal medicine, surgery, radiology, and multidisciplinary programs. Most combine didactic lectures and projects assessing the outcome of various aspects of patient care, concluding with presentation of findings to other residents and faculty. These projects can be organized into a "QA elective", or carried out longitudinally over several months.

CONCLUSIONS: By reviewing published reports of QA curricula in various training programs, program directors can develop projects that fit their resources and satisfy accreditation requirements.

SUPERVISOR: Dr. A. N. Lin

Title: Quality Assurance Problems in Colonoscopy Surveillance Intervals After Polypectomy

Isaac Soo, Jason Soo, Harmke van Kooten, Eline Schreuders, Sander Veldhuyzen van Zanten

INTRODUCTION: Colonoscopy is the gold standard for adenomatous polyp identification and removal. Adherence to published guidelines for colonoscopic surveillance after colonoscopy is a quality indicator of colon cancer surveillance. The objective of this study was to determine how well physicians and patients adhere to existing guidelines for follow-up surveillance colonoscopy (SC) and to determine yield from on-time, early and late colonoscopic follow-up. METHODS: Retrospective study, medical records from 119 patients who received surveillance colonoscopy for previously identified adenomatous polyps or continued post-operative CRC follow-up. RESULTS: 55 male and 64 female patients were included. Average age was 59 ± 11 years. 48/119 (40%) of recommendations from gastroenterologists were to have procedures done sooner, 2/119 (7%) later and 69/119 (53%) as expected when compared to Canadian Association of Gastroenterology Guideline 2002. For the patients who received SC earlier than guideline suggestions, 36/48 (75%) were without notable pathology. 10/48 (21%) had 1-2 adenomas < 1cm in size and 2 (4%) had a sub-centimeter tuberovillous adenoma. No adenocarcinoma was identified. Most prevalent reasons for early examination included: poor prep (n=10), incorrect SC interval based on either family history or finding of adenomas / CRC (n=10), and recommendation made prior to the availability of pathology report (n=8). For patients who received the appropriate recommendation, 12/69 (17%) patients received endoscopy 30 days within the suggested follow-up date, 22 (32%) from 3-6 months, 7 (10%) from 6-12 months and 19 (28%) over a year from the time suggested by the gastroenterologist. 6 patients had not yet had a follow-up endoscopy. CONCLUSIONS: A significant proportion of patients are suggested to have surveillance colonoscopy earlier than guideline recommendations, the majority of which have normal findings. Despite appropriate recommendations, a significant proportion of patients do not receive surveillance colonoscopy at suggested intervals. There is room for significant improvement in endosocopy resource utilization in colon cancer screening and adherence to suggested SC intervals. SUPERVISORS: Dr. Sander Van Zanten

Role of Cardiac Magnetic Resonance Imaging In The Diagnosis And Prognosis of Ventricular Arrhythmias

Nakul Sharma, Mikael Hanninen, Alfredo Pantano, Ian Paterson

Background

Many patients with malignant cardiac arrhythmias' require thorough investigations to determine the etiology. CMR is recommended as a screening tool for arrhythmogenic cardiomyopathies and has been used to guide electrophysiologic therapy

Hypothesis

CMR will detect abnormalities in a significant proportion of patients with serious malignant arrhythmias. These abnormal CMR findings are used guide therapy

Methods

We performed a retrospective review of patients > 18 years of age who had undergone CMR from 2006-2010 as part of a work-up for ventricular arrhythmias at the University of Alberta Hospital. All patients had undergone a comprehensive CMR scan on 1.5T magnet that included an assessment of ventricular volumes, mass, function as well as myocardial scar on late gadolinium enhancement (LGE) imaging. Patients were divided into three groups: (1) ventricular tachycardia/ventricular-fibrillation/sudden cardiac death, (2) non-sustained ventricular tachycardia/frequent premature ventricular complexes and (3) asymptomatic screening. In each group, CMR findings were compared to clinical outcomes: death, cardiac death, hospital admission, ICD implantation, and electrophysiologic ablation.

Results

211 patients were identified during the reference period of which 23 were excluded due to lack of clinical/imaging data. Across the entire group, the mean age was 44±yrs with 62% males. 84 patients underwent CMR for VT/VF, 56 for NSVT/PVCs and 48 for asymptomatic screening.

The overall frequency of an abnormal CMR was 39.4%. Gadolinium contrast was used in 82.9% (155) of cases and the prevalence of late gadolinium enhancement was 23 (X vs. Y, $P < 0.001$).

LGE was more prevalent in the group with VT/VF compared to the two other arrhythmia cohorts ($p<0.05$). No difference in LGE prevalence was seen between the NSVT/PVC and Asymptomatic Screening groups.

All other clinical outcomes were more prevalent in the VT/VF cohort compared to the other two groups ($p<0.05$). In patients with VT/VF, LGE was more common in those who received an ICD ($p<0.05$). The presence of LGE did not predict other clinical end points.

Conclusion

The diagnostic and prognostic yield of CMR in patients with VT/VF is relatively high. In lower risk patients, the role of CMR is less justified and offers uncertain benefit beyond conventional testing

TITLE: OSTEOPOROSIS MANAGEMENT IN RESPIRATORY PATIENTS: AN EVIDENCE BASED APPROACH

AUTHORS: Dr. Tripti Papneja (presenter), Dr. Ganesh Subramanian, Dr. EA Yacyshyn

INTRODUCTION: Therapeutic osteoporosis trials have focused mainly on postmenopausal women; however patient populations presenting with low bone mineral density(BMD) in respiratory clinical practice is very diverse. The purpose of this evidence-based approach is to address some of the major challenges that plague physicians when treating osteoporosis for respiratory patients using derived clinical scenarios.

METHODS: We identified several key practice challenges in the management of osteoporosis with respiratory diseases including patients with cystic fibrosis(CF), chronic obstructive pulmonary disease(COPD) on chronic steroid therapy, and post-lung transplant. We reviewed the literature for all publications in Pubmed and developed a flow chart for how best to manage bone health in patients with these respiratory comorbidities.

RESULTS: In an evidence-based review of the literature, we have determined an approach for management of these patients. Complete assessment of risk factors for low BMD and fractures and measurement of serum calcium, phosphorus, parathyroid hormone, creatinine, alkaline phosphatase, 25-hydroxyvitamin D, and possibly thyroid and gonadal function is warranted. Stopping excessive alcohol intake and smoking, minimizing falls, calcium and vitamin D supplementation, and weight-bearing exercises has been recommended. Replacement of gonadal steroids if deficient is advisable. Current evidence supports the use of oral bisphosphonates for prevention or treatment of osteoporosis in patients with CF, chronic steroid therapy, and post-lung transplant (please refer to tables 1, 2 and 3). Efficacy of IV bisphosphonate has been demonstrated in patients with CF, chronic steroid therapy, and post-organ transplant. Teriparatide has been shown to improve BMD in patients on chronic steroid therapy.

CONCLUSIONS: Studies in patients with CF, chronic steroid therapy and post-lung transplant have not been powered to look at fractures as an end-point, so treatment recommendations are based on the effects on the surrogate end-points. Multicenter RCTs with long follow-up periods are needed in these patient populations to guide osteoporosis clinical care for them.

CLINICAL IMPLICATIONS: This evidence based approach would be a useful tool for busy clinicians in managing these complex respiratory patients with low BMD.

Word count: 2170 characters + tables

Table 1: Randomized Controlled Trials in Adult Patients with Cystic Fibrosis Using Bisphosphonates.

Authors	Year	N	Inclusion BMD Criteria	Intervention	Follow-up period-months	Post-Tx BMD Change in lumbar spine	Post-Tx BMD Change in femur neck/hip	Fracture Reduction	Notes
Aris et al	2004	48*	T-score of -1 or below	Oral alendronate 10 mg/daily vs placebo	12	4.9±3.0% vs. -1.8±4.0%, p ≤ 0.001	2.9±3.2% vs -0.7±4.7%, p = 0.003	not significant	
Chapman et al.	2009	22**	T-score of -1.5 or below	IV zoledronate(Z) 2 mg every 3 months for 2 years vs placebo	24	6·14 ± 1·86% *vs.* 0·44 ± 0·10%, *P* = 0·021	4·23 ± 1·3% *vs.* –2·5 ± 1·41%, *P* = 0·0028	No fractures in either group	27 of 63 infusions led to flu-like and MSK side-effects (6 severe, 2 withdrawals).
Haworth et al.	2001	31*	Z-score of -2 or below	IV pamidronate(P) 30 mg q 3 months vs placebo	6	4.1% vs -1.7%, p=0.001	1.7% vs -1.3%, p = 0.029	Not given	severe bone pain in 73% receiving P, thus the study was stopped prematurely.
Papaioannou et al	2008	56*	T-score of -1 or below	Oral alendronate 70 mg once weekly vs placebo	12	5.20 ± 3.67% vs - 0.08 ± 3.93%, p < 0.001	2.14 ± 3.32%, vs - 1.3 ±2.70%, p < 0.001	not significant	no differences in quality of life or the number of adverse events

*All participants received supplemental oral vitamin D(800 IU) and calcium daily (1000 mg).

** calcium carbonate 600 mg and vitamin D2 1000 IU each twice daily for all participants. Prednisolone 25 mg orally per day for 3 days starting on the morning of the first infusion; repeated with subsequent infusions if a reaction to the first infusion was thought likely.

Table 2: Randomized Controlled Trials in Adult Patients on Chronic Glucocorticoid (GC) therapy* for Prevention and Treatment of Low BMD

Authors	Year	N	Inclusion BMD criteria	F/U-month	Intervention	Post-Tx changes in lumbar BMD	Post-Tx Changes in femur hip BMD	Fracture reduction	Notes
Adachi et al.	2000	141	N/A	12	intermittent cyclical etidronate vs placebo	3.7% (2.6 to 4.7) & 4.8% (2.7 to 6.9) significant change in preventive & treatment studies	1.7% (0.4 to 2.9) significant change in prevention studies; no significant change in treatment studies	In the prevention studies, ↓fracture incidence in the etidronate group vs placebo group (relative risk 0.50; CI 0.21 to 1.19)	3 Prevention studies and 2 treatment studies pooled analysis
Cranney et al.	1999	441	N/A	12	Calcitonin vs placebo	Weighted mean difference 3.2% (95% CI: 0.3 to 6.1) significantat 12 months but not 24 months.	Not significant	Not significant	Meta-analysis of 9 trials; a larger effect of calcitonin on spine BMD(~6%) in treatment RCTs than prevention RCTs(~1%)
Eastell et al.	2000	120	N/A	97 weeks	risedronate 2.5 mg/d vs placebo	+1.4% vs –1.6% (p = 0.009).	-1% vs -3.6% (not significant)	Not significant	Prevention Study
Nijs et al.	2006	201	N/A	18	Daily alendronate (10 mg) vs	2.1% vs -1.9%	1.4 % vs -2.0% ;	Not significant	Preventive study with rheumatic

					alfacalcidol (1µg)	P<0.001.	p<0.001.		disease patients
Reid et al.	2009	833	2 cohorts: GC < 3 months or GC > 3 months.	12	5 mg IV zoledronic acid versus 5 mg oral risedronate	4·06% [SE 0·28] *vs* 2·71% [SE 0·28], p=0·0001	1.45% [SE 0.31] vs 0.39% [SE 0.30], p=0.005	not significant	For prevention group: LS 2·60% [0·45] *vs* 0·64% [0·46], p<0·0001)
Saag et al.	1998	477	N/A	48 weeks	alendronate vs placebo	2.9% vs -0.4 % ; p≤0.001	1.0 % vs -1.2%; p≤0.01	Not significant	Prevention Study
Saag et al.	2009	428	T score ≤ -2	36	teriparatide 20 µg/day vs alendronate 10 mg/day	11.0% vs 5.3% for lumbar spine (p < 0.001)	6.3% versus 3.4% for femoral neck (P < 0.001)	↓Vertebral fractures: 1.7% vs7.7%, P=0.007	Treatment study
Sato et al.	2003	102	N/A	144 weeks	Didronel vs placebo.	4.8 +/- 6.9% vs 0.4 +/- 5.0% (p<0.01)	Not given	Not Significant	Treatment Study. All received 0.75 µg/day alphacalcidiol
Stoch et al.	2009	173	T-score < – 2.5	12	alendronate 70 mg q weekly	2.45% vs – 0.57%, p ≤ 0.001	0.75% vs – 0.44% , p = 0.008	Not significant	Treatment study
Tascioglu et al.	2005	50	T-score <- 2.5	24	alendronate 10 mg/day vs calcitonin	4.34% vs 1.75%; p<0.05	2.52% vs -3.76%; p=0.001	Not significant	Post-menopausal RA patients on GC >6 months
Wallach et al.	2000	518	N/A	12	risedronate 5 mg or placebo daily	1.9 ±0.38 vs -1.0 ± 0.4%, p<0.001	1.3 ±0.40 vs -1.5 ±0.4%, p<0.001	↓ 70% in vertebral fracture risk ; p=0.01	Combination of two prevention studies

*2.5-7.5 mg of prednisone or equivalent therapy for at least 3 months. All patients received calcium and vitamin D supplements. IV Pamidronate has been shown to prevent GC induced bone loss, but has not been approved for this purpose

Authors (publication year)	n	Inclusion BMD Criteria	Intervention	Follow-up period - months	Post-Tx BMD Change in lumbar spine	Post-Tx BMD Change in Femur neck/hip	Fracture Reduction	Notes
Aris et al. (2000)	37*	spine T-score of -3.0	Pamidronate 30 mg IV every 3 months vs placebo	24	8.8 ± 2.5% vs 2.6 ± 3.2%, p ≤ 0.015	8.2 ± 3.8% vs 0.3±2.2 %, p ≤ 0.015	not significant	CF patients only.
Braith et al. (2007)	30*	none	Alendronate(A) 10 mg/d or (A) 10 mg daily plus resistance training (A+RT)	8	1.4 ± 1.1% in alendronate group vs -14.1 ± 3.9%	Not given	Not given	A + RT had a greater increase in lumbar BMD, 10.8 ± 2.3%
Henderson et al. (2001)– included cardiac (n=31) & lung (n=10) transplant	41*	none	Didrocal pack vs calcitriol 0.5 µg/d for 6 months	12	1.03 ± 0.14 vs 1.07 ± 0.20 (not significant)	0.82 ± 0.11 vs 0.84 ± 0.14 (not significant)	Not significant	Etidronate provided protective carryover at 12 months and 2 years, ($p \leq 0.05$).

*All participants received supplemental oral vitamin D(800 IU) and calcium daily (1000 mg).

Definition and Predictors of Abnormal Bone Mineral Density in Severe Obesity

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INTRODUCTION: The range of bone mineral density (BMD) values in patients with severe obesity has not been well studied. Often, BMD measurements in severely obese patients are compared to the normal weight population. A severely obese individual may have a BMD that is well above the normal population average and yet markedly lower than other severely obese individuals.

METHODS: A cross-sectional study of 400 severely obese (mean age 44.1 years and BMI range 35-65 kg/m^2) women admitted to the Edmonton Weight Wise program between November, 2008 and June, 2010. Dual-energy X-ray absorptiometry (DXA)-ascertained BMD measurements (t-scores and BMD in g/cm^2) were collected from total spine, total hip, femoral neck and trochanter sites. Patients on bisphosphonates, oral estrogen, and glucocorticoids at the time of DXA were excluded. We examined the relationship between BMD and BMI in this population and across age strata (<30 yr, 30-39 yr, 40-49 yr, 50-59 yr, and >59 yr).

RESULTS: DXA BMD measurements were collected from 400 women aged 21 to 77 years with BMI 35-65 kg/m2. Higher BMI was associated with increased femoral neck BMD in age cohorts up to 50 years, after which the BMI effect was negligible and even showed decreased BMD related to BMI (>59 yr).

CONCLUSIONS: Higher BMI may not be associated with increased BMD for women of all ages. Obesity may not always be considered protective for BMD, especially in women over the age of 50 yr. Future work is planned to more clearly define and indentify predictors of low BMD in obese women.

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Pseudallescheria boydii complex Wrist Septic Arthritis/Osteomyelitis in a Patient with Rheumatoid Arthritis Receiving Etanercept

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Background: With the growing use of monoclonal antibody therapies to treat various inflammatory and autoimmune conditions, an increasing number of infectious complications are being reported.

Case: A 52 year old man with rheumatoid arthritis treated with methotrexate, leflunomide, and etanercept presented with acute painful swelling over the right wrist several days after having received an intra-articular triamcinolone injection into his wrist. Ultrasound guided aspiration of the wrist compartments revealed fungal elements on gram stain. On operative exploration, there was noted to be extensive infection of the fourth, fifth, and sixth compartments of the wrist as well as the entire extensor retinaculum. Moderate amounts of purulent material were sent for culture which grew a fungus identified as *P. boydii* complex. The patient was started on combination therapy with voriconazole and terbinafine for *P. boydii* complex osteomyelitis of the wrist. Therapy with etanercept was stopped. We questioned whether the infection was introduced into the wrist via the triamcinolone injection. At 1 year post debridement, the patient is doing well but has developed extensive fibrotic tissue in the area of the previous debridement.

Discussion: *Pseudallescheria boydii* is a ubiquitous saphrophytic fungus that is known to cause infections in both immunocompetent and immunocompromised hosts. To our knowledge, this is the first osteoarticular infection by *P. boydii* complicating the use of etanercept in the treatment of an inflammatory condition. It is important that clinicians be aware of *P. boydii* as a cause of osteomyelitis and septic arthritis in patients receiving therapy with monoclonal antibodies, treatment for which (based on previous case reviews) is a combination of surgical debridement with antifungal therapy for an extended period.

Bordetella holmesii Bacteremia in Northern Alberta: A 5-year Case Review

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Introduction: *Bordetella holmesii* is an emerging pathogen that can invasive disease in immunocompromised (particularly asplenic) patients. Due to the fastidious growth requirements of this organism, it can be difficult to identify in the routine microbiology laboratory. The aim of this study was to carry out a 5-year review of *B. holmesii* cases in Northern Alberta.

Methods: Cases of *B. holmesii* bacteremia were identified retrospectively at the Provincial Laboratory for Public Health (Microbiology) at the University of Alberta Hospital. Blood culture isolates referred for identification to the Provincial Laboratory by DYNALife Microbiology Laboratories during the pre-identified 5-year period were also included in our review.

Results: From October 2005 – November 2010, 8 cases of *B. holmesii* bacteremia were identified. 50% were from the Edmonton region and one case was from the Northwest Territories. The average age was 43 years (range 4 weeks – 66 years) and 62.5% were male. Identified comorbidities included ulcerative colitis on prednisone (2 patients), asplenia, common variable immune deficiency, and type 2 diabetes mellitus. Cough, fever, and upper respiratory tract symptoms were the presenting manifestations in 50% of patients. The organism usually grows poorly on blood-agar plates, but the growth can be enhanced by incubating plates at 80-90% humidity for 24-48 hours. Identification was confirmed using biochemical testing, cellular fatty acid analysis, and confirmation by sequencing at the National Microbiology Laboratory (Winnipeg, Manitoba). The most effective antibiotics were found to be ciprofloxacin, levofloxacin, meropenem, and imipenem. None of the patients reviewed died from *B. holmesii* infection.

Conclusions: *B. holmesii* can cause infections in both healthy and immunocompromised individuals. Although it is an organism of low virulence and susceptible to many common antimicrobials, infection with *B. holmesii* can cause severe sepsis. The organism can be difficult to initially identify if not grown in high humidity which may delay identification.