Summary of results Although there was a general consensus concerning pain, there were some notable differences. Although clinicians believed that only 8% of HS patients had symptoms of depression, more than twice that percentage of patients mentioned these concerns. Also, the 3rd most common complaint was frustration with healthcare professionals, but this was expected to be 11th out of 15.

Conclusions HS is a difficult disease to treat. Clinicians may need to be more aware of HS patient's symptoms of depression and their difficulties navigating through the healthcare system. With these potential improvements in HS patient care, online patient forums are shown to be a valuable tool.

Adolescent medicine and general paediatrics II

Concurrent session

Friday, January 26, 2018

8:00 AM – 10:00 AM

224 PIERCING REMAINS A SIGNIFICANT RISK FACTOR FOR NICKEL CONTACT DERMATITIS; PRELIMINARY RESULTS FROM AN ONLINE SURVEY

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10.1136/jim-2017-000663.224

Purpose of study Survey prevalence and demographics of piercings and self-reported nickel sensitivity in the United States.

Methods used The Nickel Contact Dermatitis Survey is a self-reporting, online questionnaire developed to gather information regarding the prevalence of nickel allergic dermatitis. Social media outlets such as Facebook, Twitter, Instagram, Reddit, and YouTube were utilised to broadcast an online version of the survey. Additionally, a paper version was distributed at local universities.

Summary of results Between Jun 1- September 25, 462 respondents in the United States were indexed. A chi-squared test comparing pierced individuals (n=319) and those with a self-reported nickel sensitivity (n=198) reveals a statistically significant correlation (X-squared=70.49, df=1, p-value<2.2e-16), consistent with previous research in this area. Additional statistical analysis reveals attributable risk of 44% for piercing and nickel sensitivity.

Conclusions The strong association between piercing and nickel sensitisation underscores the importance that health care practitioners and the public understand that piercing remains a risk factor for lifelong nickel sensitivity.

225 MOTIVATIONAL INTERVIEWING TO TREAT OVERWEIGHT AND OBESE ADOLESCENTS: A SYSTEMATIC REVIEW

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10.1136/jim-2017-000663.225

Purpose of study Adolescent obesity is a worldwide epidemic with long term health risks, but successful treatment remains

challenging. Motivational interviewing (MI), an interventional approach designed to enhance behaviour change, shows promise in the context of healthy lifestyle changes among adults. Since the last published systematic review (SR) in 2014, 9 additional MI intervention studies targeting overweight and obesity in adolescents have been published. The goal of this SR is to update the evidence to assess the effects of MI for treating overweight and obesity in adolescents.

Methods used We developed and published a protocol (#CRD42017072342) using Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA), which describes the methodology. We used standard procedures outlined by the Cochrane Handbook for Systematic Reviews. We performed analysis for each outcome using a fixed effect model; if I^2 was greater than 50%, we used a random effect model. We produced overall effect estimates and mean difference (MD) with 95% confidence intervals (CI) for each outcome. We used optimal information size (OIS) with 0.80 power to assess necessary sample size for significant MD.

Summary of results We included 10 RCTs with 1091 participants, duration of 3 to 12 months, 1 to 16 sessions, and sample sizes of 21 to 336. There was high risk of bias due to overall lack of blinding and low to moderate quality of evidence. We found a positive effect in favour of MI in triglycerides mmol/L (MD -0.18; CI -0.36, 0.00), non-significant positive effects on body mass index (BMI) (MD -0.47; CI -1.28, 0.33), BMI%-ile (MD -1.07; CI -3.63, 1.48), BMI z-score (MD -0.04; CI -0.20, 0.13), and fasting insulin pmol/L (MD -5.43; CI -29.16, 18.29), and no effect on waist circumference, glucose, or cholesterol. The OIS necessary for detecting a statistically significant MD was not met for any outcome. Qualitative synthesis suggests MI may improve quality of life and health related behaviours, especially when added to an additional intervention.

Conclusions MI alone does not seem to be effective for treating overweight and obesity in adolescents. Results should be interpreted with caution due to overall small sample sizes. Larger studies of longer duration may be needed to assess use of MI to treat adolescent obesity.

226 DOES THE PRIMARY LANGUAGE SPOKEN IN THE HOME AFFECT IF GUARDIANS DISCUSS INGREDIENTS/FOOD LABELS WITH THEIR CHILD?

E Williams*, AJ Smith, E Pak, CM Abreu, NM Malika, E Medina, M Baum. Loma Linda University, Loma Linda, CA

10.1136/jim-2017-000663.226

Purpose of study Roughly 41% of the population within San Bernardino county speaks a language other than English at home. Although research suggests that reading food labels can lead to positive dietary choices, current FDA food labelling regulations only require bilingual food labelling if the food item is intended to gain the attention of a person who does not speak English. Thus, most food items sold in U.S. stores are solely in English. This study evaluates if the primary language spoken in the home affects whether guardians discuss food labels with their child.

Methods used Children ages 9–15 years old were referred from paediatric clinics in San Bernardino county. The children participated in Operation Fit, a day camp aimed at exposing kids at risk for or struggling with unhealthy weight

(BMI >85 th percentile) to healthier lifestyle principles. Parents completed a survey that included a question about the primary language spoken in the home and the frequency the guardian discussed ingredients and food labels with their child.

Summary of results A logistics regression for a sample size of $n=567$ was used to determine if the language spoken in the home affects the discussion of ingredients/food labels. When all the variables are held constant, Hispanics are 1.93 units more likely ($p=0.008$) to discuss food labels with their children compared to Caucasians. The odds of discussing food labels with children is expected to increase by 1.46 units ($p=0.005$) for those that speak English at home, while it is expected to decrease by 0.64 units ($p=0.004$) for those who only speak Spanish.

Conclusions Primary language spoken in the home does affect guardian-child discussions. In this population Hispanics were more likely to discuss food labels than Caucasians, but those speaking only Spanish at home were less likely to do so. This study highlights a potential barrier to access of nutrition information. Future studies of this population should look at the likelihood of ingredient/label discussions if the label is in the primary language of the consumer. Additional advocacy with the FDA could affect linguistic labelling of high fat, high calorie food.

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SEXUAL MINORITY YOUTH WHO USE SCHOOL-BASED HEALTH CENTRES REPORT ON SUBSTANCE USE AND QUALITY OF CARE

DV Rosero*, R Sebastian, MM Ramos. *University of New Mexico, Albuquerque, NM*

10.1136/jim-2017-000663.227

Purpose of study Sexual minority youth have disparate health risks compared with their heterosexual peers including higher rates of substance use. School-based health centres (SBHCs) are important access points for behavioural health services, including substance use care for sexual minority youth. This study assessed substance use prevalence and quality of related healthcare services reported by sexual minority youth who use SBHCs.

Methods used We analysed 2015 data from the New Mexico Department of Health SBHC Program. De-identified data collected through an electronic post-clinic visit survey were analysed to compare self-reported substance use and quality of healthcare for sexual minority and heterosexual youth. Quality of care measures included measures of patient-centred care and reported receipt of anticipatory guidance. We conducted bivariate and multivariate analyses.

Summary of results Of the 1233 high school students who completed surveys, 1182 (95.9%) identified their sexual orientation and were included for analysis. Among these, 166 (14.0%) self-identified as lesbian, gay, bisexual, or questioning (LGBQ) and 1016 (86.0%) self-identified as heterosexual. Among LGBQ students, 54.9% were at risk for depression compared to 30.7% of heterosexual students ($p<0.001$). LGBQ students were more likely than their heterosexual peers to report past 30 day use of alcohol ($p<0.005$), marijuana ($p<0.001$) and prescription drugs ($p<0.05$). LGBQ youth were also more likely to report unmet needs for anticipatory guidance on substance use ($p<0.005$), emotional well-being

($p<0.05$) and academic and social competence topics ($p<0.005$). Yet, LGBQ respondents had patient-centred care scores that were similar to those of heterosexual students. In logistic regression analysis, students reporting receipt of patient-centred care were found to have less unmet needs for guidance (aOR 0.420; $p<0.001$), regardless of sexual orientation.

Conclusions A substantial proportion of youth who access SBHCs identify as LGBQ and have higher behavioural health needs, however, providing patient-centred care appears protective. It may reduce unmet needs for anticipatory behavioural health guidance for LGBQ youth.

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LIPSCHÜTZ ULCER – THE UNCOMMON DIAGNOSIS OF EXCLUSION

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10.1136/jim-2017-000663.228

Case report Patient is an 11 year-old female with a history of recurrent oral ulcers and ADHD, with initial symptoms of a fever, sore throat and headache a week prior. A few days later, after symptom resolution, she developed pruritic labial swelling and grey vaginal discharge followed by two painful ulcerations on her labia minora. She was prescribed amoxicillin clavulanate and referred to a gynaecologist where vaginal cultures and ulcer swabs were performed. She also received a dose of azithromycin and was started on valacyclovir. She had no improvement, developed significant dysuria and urinary retention, prompting admission.

History was negative for abuse and no past history of genital lesions. Ulcers were approximately 2 cm, bilateral and symmetric with an overlying greyish exudate and associated swelling of the labia minora.

Therapeutic modalities tried due to working diagnosis of Behçet's, per rheumatology, included prednisone and topical flononide initially and then IV pulse methylprednisone, all with no improvement. With a negative ophthalmological exam for uveitis and negative autoimmune serology as well, this was ruled out. Of note patient was later found to be HLA B51 positive. ID modalities included CMV and EBV testing and initiating IV Acyclovir pending HSV. Positive results of elevated EBV IgM narrowed the diagnosis to Lipschütz ulcers or ulcus valvae acutum.

This is an uncommon self-limited genital ulceration in non-sexually active adolescent females. Ulcers are deep with a violaceous border and necrotic base covered with a grey exudate. It is a diagnosis of exclusion and proposed criteria for diagnosis of Lipschütz ulcer in a young female with a recent viral illness includes first episode of acute genital ulceration, age <20, presence of deep, well-delimited, painful ulcerations on the labia, characteristic bilateral 'kissing pattern', absence of sexual contact, and exclusion of other known causes of genital ulceration. In this particular case, the evidence of acute EBV infection supported the diagnosis of Lipschütz ulcer in the setting of a primary EBV infection. This association has been reported in the past in limited case reports, particularly in gynaecology literature. It is considered rare but may be an overlooked diagnosis and should prompt early recognition and a systematic work-up to rule in this self-limited disease.

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THE ROLE OF REST IN RECOVERY AFTER CONCUSSION: A COMPREHENSIVE LITERATURE REVIEW IN CHILDREN AND ADOLESCENTS

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10.1136/jim-2017-000663.229

Purpose of study Historically, rest has been the mainstay of concussion treatment. Yet 'rest' remains poorly defined, resulting in a lack of data demonstrating that resting after concussions leads to improved outcomes. Our study investigates the effects of physical and cognitive rest on outcomes in paediatric populations in order to clarify current concussion treatment guidelines.

Methods used A systematic literature review was done through PubMed, an online database. Only controlled studies that included two groups (Rest and Activity) with clear definitions

of rest in paediatric and adolescent patients (ages 5–22) were included in our analysis.

Summary of results Six studies met our inclusion criteria (see table 1). Levels of activity were defined differently in various studies. In general, immediate removal from play seemed to be helpful in shortening concussion recovery time. However, incorporating physical activity within 7 days of a concussion resulted in improved outcomes. There was no significant difference in outcomes in patients who rested a full 5–7 days when compared to patients who returned to activity as individually tolerated. In addition, patients with medium levels of activity had better recovery.

Conclusions Our review shows that extremes of strict cognitive rest or immediate return to full physical activity may have a negative impact on the duration of post-concussive symptoms and the duration of recovery. Physicians should individualise the care of post-concussion patients and avoid recommending placing extreme limitations on physical or cognitive activities. Future prospective studies that objectively quantify both cognitive and physical exertion after concussion are needed.

Abstract 229 Table 1

Source	Definition of rest	Definition of activity	Evaluation of concussion symptoms	Definition of primary outcome	Primary outcome		P-value
					Rest	Activity	
Grool A, (2016)	No physical activity	Physical activity within 7 days after concussion	Post-Concussion Symptom Inventory (PCSI)	3+new or worsening symptoms 28 days after concussion	320/736 (43%)	413/1677 (25%)	<0.05
Elbin (2016)	Immediate removal from sports after sports-related concussion (SRC)	Continued to play sports after SRC	Immediate Post-Concussion Assessment and Cognitive Test (ImPACT)	Protracted recovery of ≥ 21 days	10/32 (31%)	24/30 (80%)	0.003
Thomas (2015)	No school, work, or physical activity for 5 days	1–2 days of subjective rest with stepwise return to activity	ImPACT, Post-Concussive Symptoms Scale (PCSS)	Symptom resolution 10 days after	28/45 (63%)	29/43 (67%)	0.82
Buckley (2016)	Cognitive and physical rest for 7 days	Not excused from normal school activities, including exercise and sports	Standard Assessment of Concussion (SAC), Balance Error Scoring System (BESS), graded symptom checklist (GSC), ImPACT, computerised neuropsychological tests (CNT)	Time to asymptomatic status (patient-reported)	n=25 5.2 $\pm$ 2.9 days	n=25 3.9 $\pm$ 1.9 days	0.047
				Time to clinical recovery (days until all tests at baseline)	6.8 $\pm$ 4.6 days	7.2 $\pm$ 5.8 days	0.809
Gibson (2013)	Cognitive rest specifically recommended	Cognitive rest not specifically mentioned at discharge	PCSS	Mean symptom duration (days until PCSS=0)	n=85 57 days	n=50 29 days	<0.05
Majerske (2008)	No school or exercise activity	School activity and participation in sports – Activity Intensity Scores (AIS) 0–4	ImPACT, Colorado Concussion Scale	Visual Memory category of ImPACT, percentile score	n=35, AIS 0	33.00*	0.003
					n=77, AIS 1	46.81	
					n=57, AIS 2	52.39	
					n=26, AIS 3	24.83	
					n=9, AIS 4	4.95	
				Reaction Time Category of ImPACT, percentile score	AIS 0	38.21	0.0005
					AIS 1	31.92	
					AIS 2	40.13	
	AIS 3	31.56					
	AIS 4	<0.20					

*Percentile

Cardiovascular III – cardiac disease and regeneration

Concurrent session

Friday, January 27, 2017

8:00 AM – 10:00 AM

230 HYPERGLYCEMIA FOR PROMOTING CARDIAC REGENERATION

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10.1136/jim-2017-000663.230

Purpose of study Heart failure is the leading cause of death worldwide and can develop after an ischaemic injury to the heart as seen in myocardial ischemia or as a complication of congenital heart disease. In the last 10 years, the field of cardiac regeneration has seen huge advances, allowing for the discovery of strategies that can reverse cardiac injury. Our lab is focused on non-genetic mechanisms by which this regenerative capacity could be lengthened or enhanced. Specifically, we are interested in the cyto-protective effects of glucose in cardiomyocyte proliferation. Our preliminary data has shown that glucose induces cardiomyocyte proliferation and inhibits cardiomyocyte maturation via the Pentose Phosphate Pathway (deoxynucleotide biosynthesis pathway) in a dose-dependent manner by human embryonic stem cell-derived cardiomyocytes (*in vitro*). However, whether this pathway can be a therapeutic target for heart regeneration is unknown. Our hypothesis is that glucose promotes neonatal mouse heart regeneration via regulation of nucleotide synthesis.

Methods used Non-transmural cryoinjury was successfully established and performed to the apex of the left ventricle in wild-type pups and overexpression of Glucose Transporter 1 pups, which have glucose overdose in cardiomyocytes. In the acute phase, the level of cardiomyocyte cell proliferation was measured by using flow cytometry analysis and immunostaining with PH3 and MEF2. In the chronic phase, we quantified the level of fibrosis by histology (H and E and Picrosirius Red) and neovascularization by immunostaining with CD31 (PECAM).

Summary of results Increased level of cardiomyocyte proliferation was observed in the Transgenic Glut1 pups. When analysing the level of fibrosis at P7 vs P14 stage, we have found that quantification of fibrosis seems to be worsen in the Glut 1 hearts when compared to Wild type control hearts.

Conclusions The proposed study would be the first to demonstrate the potential role of glucose as a promoter for cardiac regeneration as well as reveal a potential mechanism for congenital cardiomyopathy associated with diabetic pregnancy.

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TREATMENT WITH UNDIFFERENTIATED INDUCED PLURIPOTENT STEM CELL CARDIAC GRAFT DOES NOT WORSEN CARDIAC FUNCTION IN RAT MODEL OF CHRONIC HEART FAILURE (CHF)

SK Khalsa*, PJ Ramos, S Daugherty, M Stansifer, E Juneman, JW Koevary, S Goldman, J Lancaster. University of Arizona, Tucson, AZ

10.1136/jim-2017-000663.231

Purpose of study Induced pluripotent stem cell derived therapies hold potential to treat human disease, especially cardiovascular disease. To date, the safety of these therapies has not been satisfactorily addressed. This study was designed to assess if implantation of a cardiac graft seeded with fibroblasts and undifferentiated human induced pluripotent stem cells (uhiPSCs) in a rat model of CHF alters cardiac function.

Methods used Male Sprague Dawley rats (n=7) underwent coronary artery ligation, allowed 3 weeks to develop CHF, underwent echocardiography and were treated with a cardiac graft seeded with fibroblasts and uhiPSCs. At 7 weeks post-treatment, echocardiograms were repeated. Results were compared to control groups: heart failure n=8 (sternotomy x2, coronary ligation, no graft) and sham n=12 (sternotomy x2, no coronary ligation, no graft).

Summary of results The sham group had the best cardiac function of all three groups with higher EF, e' and e'/a' and lower E/e' compared to CHF control (p<0.05). The treatment group showed no difference compared to the untreated heart failure control group in EF, e', or E/e'. The e'/a' ratio, the ratio of peak velocity at early diastole (e') to peak velocity at late diastole (a'), improved from 1.1 in the heart failure control group to 2.0 in the treatment group (p=0.01). The difference between e'/a' of the treatment group vs the sham group was not significant.

Conclusions This study is an important step in establishing the safety of regenerative medicine treatments utilising terminally differentiated iPSCs. As there is the potential for terminally differentiated iPSC treatments to have some level of undifferentiated cell contamination, the safety of fully dosed undifferentiated cell therapies alone must be established. We found no decline in cardiac function after treatment with a cardiac graft seeded with undifferentiated hiPSCs, and in one measure (e'/a'), cardiac function actually improved. These results indicate that potential contamination of differentiated cell therapies with uhiPSCs is not a safety concern for cardiac function.

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RISK FACTORS AND MYOCARDIAL TRIGLYCERIDE CONTENT IN WOMEN'S HEART DISEASE

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10.1136/jim-2017-000663.232

Purpose of study To determine the relationship between cardiovascular risk factors and myocardial triglyceride content (mTG) in three cohorts within the Women's Ischemia Syndrome Evaluation (WISE) and Heart Failure with Preserved Ejection Fraction (HFpEF) study.

Methods used Forty patients were stratified into three groups, women with suspected Coronary Microvascular Dysfunction, men and women with a diagnosis of HFpEF, and reference control women. Subjects underwent a ^1H Magnetic Resonance Spectroscopy to determine presence of myocardial stenosis. Subjects then underwent a transmural cardiac Myocardial Perfusion Reserve Index during stress cardiac MRI to assess the presence of coronary microvascular ischemia. Subject data was stratified into abnormal and normal content data then compared using an unpaired t-test and a one-way ANOVA test to determine statistical significance of risk factors.

Summary of results Analysing common cardiovascular risk factors such as age, weight, BMI, blood glucose levels, triglyceride levels, hypertension, history of smoking, etc., the only risk factor that showed a statistical significance towards mTG content is a higher body mass index with a 0.032 p-value. Furthermore, we observed no statistical significance in mTG level across the three cohorts of the study. We observed no statistical significance to show a correlation between ischemia and increased mTG content.

Conclusions Overall, BMI is the only significant risk factor associated with an increased mTG content; however, the study is currently underpowered to fully evaluate risk factor associations. The data for the limited number of patients may suggest that mTG content may be a potential new non-invasive marker of HFpEF. However, due to small sample size, no definitive mechanistic pathway can be concluded to determine precise risk factors for increased mTG content.

233 DOES CHRONIC DISEASE AND EPIDEMIOLOGY IMPACT SEVERITY OF HEART FAILURE IN METHAMPHETAMINE CARDIOMYOPATHY?

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10.1136/jim-2017-000663.233

Purpose of study Heart failure is a chronic disease that can progress and lead to hospitalisation(s). Methamphetamine is a commonly used recreational drug and has been reports of associations with cardiomyopathy. The objective of this study was to describe the chronic disease and epidemiology on methamphetamine cardiomyopathy and to objectify the reversibility.

Methods used Data Collection –In this retrospective study, 116 patients were identified with inclusion criteria of having methamphetamine cardiomyopathy, left ventricular ejection fraction $\leq 40\%$ and age ≥ 18 .

Data was collected through uniform query of community hospital database on patient demographics, medical history, social history, number of heart failure hospitalizations, and cardiac imaging.

Summary of results Of the 116 identified patients, 53 patients (46%) had improvement of left ventricular ejection fraction

with cessation of methamphetamine use and adherence to guideline-directed therapy. Of the 53 patients 83% (47/53) were males. Twenty-three percent (12/53) had BMI less than 25% and 23% (12/53) were super obese (BMI >40). Diabetes mellitus was a co-morbidity for 32% (17/53) of the patients and of these, 88% (15/17) had improvement of left ventricular ejection fraction $\geq 40\%$ after drug cessation and medical therapy. Tobacco dependence existed in 81% (43/53) of the patients and alcohol use in 47% (25/53). Forty-five percent (24/53) had at least 2 heart failure exacerbation hospitalizations. Of the patients identified with 3 or greater heart failure exacerbation hospitalizations, 75% (39/53) had hypertension. After cessation of methamphetamines, 69% (37/53) of patients had complete reversibility of left ventricular ejection fraction (left ventricular ejection fraction $\geq 40\%$).

Conclusions Hypertension was the most common co-morbidity. Despite having hypertension, diabetes mellitus, and/or dyslipidemia, patients were able to have improvement in heart failure. Methamphetamine cardiomyopathy related hospitalisation and morbidity can decrease with medical therapy and cessation of drug use. Further studies are warranted to improve understanding of methamphetamine cardiomyopathy.

234 MULTI-DRUG RESISTANT INFECTION AFTER HEART TRANSPLANTATION: HOW SERIOUS IS THIS?

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10.1136/jim-2017-000663.234

Purpose of study In heart transplantation (HTx), rejection and infection are major causes of mortality in the first yr. It is not uncommon for patients (pts) to have multi-drug resistant infection (MDRI), particularly with prolonged intensive care unit stay. Outcome of these pts has not been clearly delineated.

Methods used Between 2010–2016, we assessed 688 HTx pts for MDRI within the first-yr post-HTx. These pts were assessed for 30 day and 1 year survival. Type of infection and drug resistance were determined. Days in ICU and hospital length of stay was assessed. 1 year freedom from rejection was noted in these pts. A control population with no infections post-HTx was included (n=191).

Summary of results MDRI was seen in 3.5% (24/688) of pts within the first-year post-HTx. The most common MDRI were Klebsiella, Pseudomonas, Acinetobacter, VRE, and MRSA. These pts had significantly longer ICU ($p<0.001$) and hospital stays ($p<0.001$). MDRI were seen in lungs, abdomen and wound sites. There was no significant difference in 30 day survival. However, pts with MDRI had significantly lower 1 year survival (69.1% vs 86.6%, $p=0.044$). There was no significant difference in any type of subsequent rejection between the two groups. 50% (12/24) of pts with MDRI post-HTx developed a subsequent infection within one yr.

Conclusions MDRI is a serious problem after HTx but fortunately is rare. Risk factors include longer ICU and hospital stays. MDRI appears to result in a higher mortality rate at one yr. Strategies to prevent MDRI are being pursued.

Abstract 234 Table 1

Endpoints	Multi-drug resistant infection (n=24)	No infections (n=191)	P-value
Type of Infection			
% VRE	12.5% (3/24)		
% MRSA	12.5% (3/24)		
% Klebsiella	16.7% (4/24)		
% Enterobacter	4.2% (1/24)		
% Pseudomonas	16.7% (4/24)		
% Acinetobacter	16.7% (4/24)		
% Other	20.8% (5/24)		
Length of Hospital Stay (days)	26.4±25.9	10.9±5.4	<0.001
Length of ICU Stay (days)	15.3±15.5	5.6±4.1	<0.001
30 Day Subsequent Survival	91.7%	92.7%	0.865
Subsequent 1 Year Survival	69.1%	86.6%	0.044
Subsequent 1 Year Freedom from Any-Treated Rejection	84.1%	84.8%	0.984
Subsequent 1 Year Freedom from Acute Cellular Rejection	88.8%	90.0%	0.976
Subsequent 1 Year Freedom from Antibody-Mediated Rejection	100.0%	95.8%	0.309

235 ASTHMA REDUCES CARDIOSCLAR RISK IN TYPE 2 DIABETES

MD Ehrhart*, C Murray-Krezan, MR Burge. *University of New Mexico Health Sciences Centre, Albuquerque, NM*

10.1136/jim-2017-000663.235

Purpose of study Type 2 diabetes (T2D) and asthma frequently occur together, and both are independent risk factors for cardiovascular disease (CVD). The CVD risk implications for patients who have both conditions, however, have not been quantitated. The ACC/AHA Cardiovascular Risk Score equation estimates the 10 year risk of a major CVD event using validated biomarkers and clinical indicators, including age, sex, race, total and HDL cholesterol, triglycerides, blood pressure, smoking status, and the presence or absence of diabetes. Using this instrument, we hypothesised that people with both T2D plus Asthma would have a significantly higher 10 year risk for a major CVD event than people with T2D Alone.

Methods used Data were extracted from the Electronic Medical Record at UNM HSC using ICD-9 codes and a standard database query. Patients with both T2D and Asthma (n=603) were identified and matched by age sex to a group of patients with T2D alone (n=603). Other respiratory diagnoses, such as COPD or cystic fibrosis, were excluded from analysis. Least squares mean estimates for the 10 year risk of a major CVD event using the ACC/AHA Cardiovascular Risk score were compared using weighted generalised linear modelling.

Summary of results As shown in the table 1, BMI was higher in the T2D plus Asthma group, and the groups also differed with respect to Race and Ethnicity, but the they were otherwise similar with respect to their descriptive characteristics. CVD risk was higher in the T2D Alone cohort (4.7%, 95% CI: 4.5% to 5.0%) as compared to the T2D plus Asthma cohort (4.5%, 95% CI: 4.3% to 4.7%) (p=0.025).

Conclusions In this matched, case control, retrospective study, individuals with co-morbid T2D and Asthma had a lower

10 year cardiovascular disease risk as calculated by the ACC/AHA Cardiovascular Risk Score equation than those with T2D Alone. Confirmation of this finding with actual cardiovascular outcomes is necessary.

Abstract 235 Table 1

Variable	T2D alone (n=603)	T2D+Asthma (n=603)	Variable	T2D alone (n=603)	T2D +Asthma (n=603)
Age (years)	54.7 ±10.0	54.7±10.0	SBP (mmHg)	128±17	127±15
Female Sex	433 (72%)	433 (72%)	DBP (mmHg)	74±10	74±11
BMI (kg/m ²)	34.2±8.2	36.6±9.3 *	On Anti-HTN Meds	444 (74%)	427 (71%)
Total Chol (mg/dl)	177±45	177±42	Smoker	98 (16%)	75 (12%)
HDL Chol (mg/dl)	46±15	45±13	A1c (%)	7.5±1.9	7.2±1.8
LDL Chol (mg/dl)	96±38	97±35	Race and Ethnicity:	180 (30%)	* 255 (42%)
Triglycerides (mg/dl)	189±141	183±113	NHW	396 (66%)	318 (53%)
			Hispanic	27 (4%)	30 (5%)
			Black		

*=p<0.001

236 NEONATAL HYPERBILIRUBINEMIA AFTER MECHANICAL CIRCULATORY SUPPORT

S Bhombal*, R Dasani, A Davis, DM Axelrod, RJ Wong, VK Bhutani. *Stanford University, Palo Alto, CA*

10.1136/jim-2017-000663.236

Case report Recent observation in the Lucile Packard Children's Hospital Cardiovascular Intensive Care Unit has highlighted the post-operative urgent use of phototherapy and two exchange transfusions (in a one year period). We present three cases of hyperbilirubinemia in neonates post mechanical circulatory support that required urgent intervention.

Case 1 is a full term male with prenatally diagnosed interrupted aortic arch, VSD, initially on prostaglandin (PGE). Total bilirubin (TB) level prior to surgery peaked at 14.9 mg/dL, albumin 2.3 g/dL on day of life (DOL) six. No ABO incompatibility or clinical signs of hemolysis. He was placed on cardiopulmonary bypass on DOL 6 for aortic arch reconstruction, VSD and ASD patch closure, and aortic valve commissuroplasty. He had increasing hyperbilirubinemia (TB 19 mg/dL, albumin 2.2 g/dL) despite intensive phototherapy by postoperative day three and underwent exchange transfusion.

Case 2 is a full term male with prenatally diagnosed hypoplastic left heart syndrome and restrictive atrial septum, s/p atrial septectomy, bilateral pulmonary artery (PA) banding, and placement onto venoarterial extracorporeal membrane oxygenation shortly after birth. He had increasing indirect hyperbilirubinemia on phototherapy, no ABO incompatibility, and required exchange transfusion with rapid increase from TB 22 to 28.7 mg/dL on DOL 8, albumin 2.5 g/dL.

Case 3 is a full term male postnatally diagnosed with hypoplastic left heart syndrome with severely depressed biventricular function. He underwent bilateral PA band placement on DOL 4, continued on PGE, then was placed on a ventricular assist device (VAD) on DOL 19. Bilirubin increased from 6.8

to 21.1 mg/dL, albumin 2.1 g/dL, following VAD placement, which improved on phototherapy.

Acute hyperbilirubinemia in adult patients following cardiopulmonary bypass is a known association, occurring in ~25% of patients post bypass (Sharma, 2015). There is a paucity of neonatal literature regarding such acute manifestations. These three cases highlight the issues related to increased bilirubin load from increased production or elimination. Surveillance for hyperbilirubinemia may be warranted post-procedure for neonates with congenital heart disease who require mechanical circulatory support.

Endocrinology and metabolism II

Concurrent session

Friday, January 27, 2017

8:00 AM – 10:00 AM

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PROGRAMMED ADIPOCYTES CONTRIBUTE TO OBESITY IN LOW BIRTH WEIGHT OFFSPRING: INTERACTION WITH AMBIENT TEMPERATURE AND FAT DEPOTS

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10.1136/jim-2017-000663.237

Purpose of study Maternal nutrition plays a paramount role in fetal development epigenetically, this influences the risk of offspring obesity. Specifically, maternal food-restriction (FR) during pregnancy has been shown to result in low birth newborns (LBW) that develop adult obesity, in part due to enhanced adipogenesis as a result of hyperplasia and/or hypertrophy of adipocytes. Ambient temperature (conventional 22°C; thermoneutral 30°C) is known to impact adipogenesis in both subcutaneous and visceral retroperitoneal fat. We hypothesised that adult LBW offspring will have increased adipocyte cell size and/or number, and that housing at thermoneutrality will accentuate the adiposity difference between LBW and Control offspring.

Methods used Pregnant mice were housed at either standard 22°C or thermoneutral 30°C room temperature. At gestational age e10, mice were fed either an ad libitum diet (Control) or were 30% food-restricted to produce LBW newborns. Following delivery, all mice were fed ad libitum diet. At 12 months of age, male offspring body weights and body fat were obtained, and subcutaneous and retroperitoneal adipose tissue was collected for determination of adipocyte cell size. Differences between groups were analysed using ANOVA.

Summary of results LBW male newborns were significantly growth restricted at birth (22°C: 1.80±0.04 vs 2.08±0.06 g; 30°C: 1.70±0.05 vs 1.87±0.02 g). However, adult LBW were markedly heavier than controls (22°C: 30.9±0.5 vs 27.8±0.4 g; 30°C: 32.2±0.3 vs 29.9±0.5 g) and had significantly greater percentage body fat (22°C: 13.6±1.0 vs 10.4%±1.1%; 30°C: 19.4±0.8 vs 16.5%±1.0%). LBW males had significantly increased adipocyte cell size as compared to controls, with this effect accentuated at 30°C.

Conclusions In LBW offspring, hypertrophic adipocytes likely contribute to increased fat storage and obesity. At thermoneutrality, despite birth weight being lower, the adult body weight and fat

was increased. Adipocyte cell size was larger in retroperitoneal versus subcutaneous fat, with effects accentuated by thermoneutral housing. Thus, thermogenesis-mediated effects contribute to reduced adiposity and cell size at lower temperature.

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TESTOSTERONE TREATMENT NORMALISES BODY FAT IN INFANTS WITH XXY/KLINEFELTER SYNDROME

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10.1136/jim-2017-000663.238

Purpose of study Prenatal diagnoses of 47, XXY/Klinefelter syndrome (KS) are rapidly increasing due to non-invasive prenatal screening. XXY is associated with testicular insufficiency and the metabolic syndrome even in prepubertal children. The mini-puberty period of infancy is postulated to be a critical period of testosterone exposure for programming of metabolic processes and adiposity accumulation. This testosterone surge may be lower in infants with XXY, therefore we hypothesised that testosterone treatment in would result in improved body composition.

Methods used Infants with a prenatal diagnosis of 47, XXY were enrolled between 6–15 weeks of age and randomised to receive testosterone cypionate (T) 25 mg intramuscularly every 4 weeks for 3 doses or no treatment. Body composition using air displacement plethysmography (PeaPod), growth parameters, and motor development were assessed at enrollment and at 12 weeks. Our primary outcome was change in percent body fat (%BF) z-scores between assessments. Secondary outcomes included change in lean body mass and stretched penile length, growth velocity, and side effects.

Summary of results Twenty subjects have enrolled and randomised with 18 (10 T, 8 no T) complete to date. Baseline maternal and infant factors, including age and %BF were similar between groups. Infants in the untreated group had an increase in %BF z-score of 0.9±0.7 while the T group had no change (−0.1±0.6; p=0.005). At 5 months of age, the %BF for the T group was the same as data from 316 local male controls (22.9% v 23.2), while the untreated group was significantly greater (23.2 vs 27.1, p=0.037). Growth velocity and increase in stretched penile length were also greater in the T group. There were no serious adverse effects.

Conclusions This pilot study supports that a three-month course of testosterone injections may have measureable short-term effects on body composition in infants with KS. We do not advise routine testosterone therapy in infants based on these results as our sample size is small and the long-term clinical implications of our outcome measures are uncertain. However, these results support the need for prospective, blinded, and placebo-controlled investigation to confirm these preliminary findings and determine if benefits are sustained.

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PHARMACOKINETIC AND PHARMACODYNAMIC EFFECTS OF 28 DAYS OF ORAL DIMETHANDROLONE UNDECANOATE IN HEALTHY MEN: A PROTOTYPE MALE PILL

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10.1136/jim-2017-000663.239

Purpose of study Dimethandrolone (DMA) and its undecanoate ester (DMAU) are modified testosterone (T) derivatives that have androgenic and progestational actions, suppress gonadotropins, maintain androgenic effects and inhibit spermatogenesis in pre-clinical studies. A first-in-men study showed that single oral DMAU doses of 200–800 mg, were well tolerated and reversibly suppressed serum LH and T. We assessed the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of 28 days of daily oral DMAU in healthy young men.

Methods used A phase 1b, double blind study was conducted at 2 academic medical centres. Healthy men (18–50 y) were randomised to receive either daily oral placebo or 100/200/400 mg of DMAU with food in 1 of 2 unique formulations – castor oil/benzyl benzoate (C) or powder in capsule (P). Subjects underwent 24 hour PK studies with hourly vitals, serial blood DMAU/DMA and hormone measurements on days 1 and 28 and twice weekly ambulatory visits for safety labs, hormones and drug levels. The primary outcomes were safety measures (vitals, hematocrit, liver function tests, serum lipids, EKGs and adverse events). Secondary outcomes were PK profiles and PD effects – suppression of LH, FSH and T, sexual function (per validated psychosexual diary) and mood (PHQ-9) throughout the study.

Summary of results 83 subjects completed the study. There were neither serious adverse events nor significant changes in serial safety measures, mood or sexual function in any group. 9 subjects reported decreased libido (8 drug, 1 placebo) and 8 reported acne (5 drug, 3 placebo); all resolved by study conclusion. A dose-related C_{avg} was seen at day 28 for both serum concentrations of DMAU ($p < 0.001$) and DMA ($p < 0.001$). All active treatment groups reduced serum T into the hypogonadal range (day 28 median C_{avg} 13.4 ng/dL, IQR 7.6–72.1 ng/dL). All subjects in the P400mg group And 12/13 subjects in the C400mg group Achieved suppression of both LH and FSH to < 1 IU/L.

Conclusions Daily oral administration of DMAU for 28 days in young healthy men is well tolerated. Doses of 400 mg suppress serum T to near castrate levels and maximally suppress serum LH and FSH. These promising results support further development of DMAU as a single agent oral male contraceptive pill.

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SINGLE, ESCALATING DOSE PHARMACOKINETICS, SAFETY, AND FOOD EFFECTS OF A NEW ORAL ANDROGEN 11 β -METHYL-19-NORTESTOSTERONE 17 β -DODECYLCARBONATE IN MAN: A POTENTIAL ORAL MALE HORMONAL CONTRACEPTIVE

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10.1136/jim-2017-000663.240

Purpose of study 11 β -methyl-19-nortestosterone 17 β -dodecylcarbonate (11 β -MNTDC) is an orally bioavailable prodrug of 11 β -methyl-19-nortestosterone (11 β -MNT). Given 11 β -MNT's androgenic and progestational activities, we hypothesised that 11 β -MNTDC will suppress gonadotropins and be a potential new oral male hormonal contraceptive.

Methods used We conducted a randomised, double-blind Phase I study at two academic medical centres assessing the safety, tolerability and pharmacokinetics of single escalating doses of

11 β -MNTDC (in 70:30 castor oil:benzyl benzoate gel capsules) administered orally with or without food in healthy men. For each dose of 11 β -MNTDC (100–800 mg), 10 male subjects received 11 β -MNTDC and 2 received placebo. Serial serum samples were drawn over 24 hour following each dose. **Summary of results** Oral 11 β -MNTDC doses were well tolerated and there were no serious adverse events or significant concerns in safety parameters. When administered fasting, very little 11 β -MNTDC was absorbed, and minimal concentrations of 11 β -MNT were observed regardless of the dose given. Concomitant administration of 11 β -MNTDC with a 50% fat meal markedly increased 11 β -MNTDC and 11 β -MNT average serum concentrations ($p < 0.0001$ for all doses) compared to fasting. A significant dose incremental effect on average serum drug concentrations was also observed after 11 β -MNTDC administration with food (all β coefficients positive and linear, $p < 0.0001$). Serum 11 β -MNTDC and 11 β -MNT levels were lower but measurable 24 hour after dosing. The average conversion of 11 β -MNTDC to 11 β -MNT at C_{max} was $< 0.05\%$ at all doses administered with food and the elimination half-lives averaged across all doses were 2.5 ± 0.1 hour for 11 β -MNTDC and 6.1 ± 0.3 hour for 11 β -MNT respectively. Testosterone concentrations were significantly suppressed over the 24 hour period after 11 β -MNTDC oral dosing at 200, 400, and 800 mg with food ($p < 0.002$).

Conclusions In summary, our first-in-man study demonstrated that a single, oral dose of 11 β -MNTDC up to 800 mg is safe, and that 11 β -MNTDC requires concomitant food administration for effectiveness.

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PREVENTING SECONDARY EXPOSURE TO WOMEN FROM MEN APPLYING A NOVEL MALE HORMONAL CONTRACEPTIVE GEL

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10.1136/jim-2017-000663.241

Purpose of study Testosterone (T) gel combined with nestorone (NES) gel has been shown to effectively suppress gonadotropins and spermatogenesis in men as a potential transdermal male contraceptive. Transdermal T transfers from men to women after skin to skin contact with the gel application site, which could contribute to female hirsutism and acne. Transfer can be prevented if the man washes or covers the application site with clothing. We hypothesised that male showering or wearing a shirt over the gel application site would prevent secondary transfer of T and NES to a woman after close skin contact.

Methods used 12 healthy, young male-female volunteer couples were recruited. Men applied T-62/NES-8mg gel on their shoulders and upper arms. 2 hour after the man applied the combined T/NES gel, the woman rubbed the application site for 15 min. Exposure in the female partner was assessed under 3 conditions: 1) the man wore a shirt covering the site; 2) the man showered about 15 min prior to skin contact; 3) without any intervention to reduce exposure. Female serum T and NES concentrations were measured by LC-MS/MS serially for 24 hour after gel exposure.

Summary of results Female serum T C_{avg} was 26.6 ± 9.8 (mean $\pm$ SD, $p < 0.01$) and 29.6 ± 11.6 ng/dl ($p < 0.02$) with the

shirt barrier and showering respectively which was significantly higher than baseline (21.5 ± 7.9 ng) but lower than without intervention 62.1 ± 35.7 ng/dl (both $p < 0.01$). Female NES C_{avg} was 1.1 ± 3.6 and 0.5 ± 1.6 pg/ml above baseline with the shirt barrier and showering respectively (baseline NES levels were undetectable) and appeared lower than without any intervention 8.1 ± 10.9 pg/ml. Two women had acne and menstrual flow increased in one woman with a prior history of irregular menses.

Conclusions Secondary transfer of T and NES occurs after intensive, close skin contact at the gel application site. This exposure can be decreased by a T-shirt barrier or showering before contact. Men using contraceptive transdermal gels containing T+NES or other androgens/progestins should wash before contact with a woman or child, or wear clothing over the application site to prevent transfer of the steroids to other persons.

242 EMERGING ROLES OF HIGH-DENSITY LIPOPROTEINS IN FERTILITY

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10.1136/jim-2017-000663.242

Purpose of study High-density lipoproteins (HDL) are a heterogeneous class of lipoproteins with established roles in anti-inflammation, anti-oxidation, and other protective mechanisms. Recent findings that HDL transports microRNAs and complex lipid signalling molecules suggest HDL may have a targeted role in biochemical regulation that is currently unidentified. HDL is the sole lipoprotein class present in ovarian follicular fluid (FF), the fluid that nourishes maturing oocytes prior to ovulation. Our goal is to identify the molecular properties of HDL in FF and elucidate the role of HDL in ovarian health and fertility.

Methods used Follicular fluid from women undergoing fertility treatment for diminished ovarian reserve and oocyte donors was collected taking care to avoid blood contamination. Native HDL was isolated from the samples using the selected-affinity immunosorption technique developed in our lab. The whole FF and HDL fraction was analysed for total cholesterol, triglycerides, and HDL quantity. Samples were applied to a 35-cytokine multiplex assay to quantify pro- and anti-inflammatory cytokines. Multivariate analysis was performed to compare differences in lipids and cytokine profiles in controls compared to women with infertility.

Summary of results Of 35 cytokines analysed, a majority is found to be transported by HDL in FF. The distribution of pro- and anti-inflammatory cytokines between oocyte donors and fertility treatment sources reveal a difference in FF environment that correlates with oocyte health. Results from this study suggest HDL-associated cytokine profiles contribute to the FF environment and the likelihood of fertility and successful pregnancy.

Conclusions HDL transports a number of cytokines in FF, a previously unknown quality of HDL. The cytokine expression profile differs greatly between healthy controls and women experiencing infertility. HDL appears to contribute to oocyte health and viability, thus examining the follicular fluid HDL may provide better outcomes for women seeking fertility treatment.

Gastroenterology

Concurrent session

Friday, January 27, 2017

8:00 AM – 10:00 AM

243 FREE-BREATHING MAGNETIC RESONANCE IMAGING FOR DIAGNOSIS OF PAEDIATRIC NON-ALCOHOLIC FATTY LIVER DISEASE

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10.1136/jim-2017-000663.243

Purpose of study Visceral adiposity (VAT) and hepatic fat are critical to later childhood obesity and non-alcoholic liver disease (NAFLD). While magnetic resonance imaging (MRI) can non-invasively and accurately quantify these biometrics, it requires breath-holding (BH) and sedation. As a result, current technology precludes many children. Using non-sedated free-breathing (FB)-MRI, this study's objectives were to 1) evaluate the accuracy and repeatability of FB-MRI vs BH-MRI, 2) correlate hepatic proton density fat fraction (H-PDFF,%) and VAT volume (cm^3/m^2), and 3) assess feasibility of this technology in infants.

Methods used This study had 3 groups: 1) healthy controls (CON), ages 6–17 years, body mass index (BMI) $<85\%$, 2) NAFLD subjects, ages 6–17 years with suspected NAFLD, BMI $>85\%$, and 3) infants, 28 days – 1 year of age. CON and NAFLD subjects underwent BH- and FB-MRI. Infants underwent FB-MRI.

Summary of results 10 CON, 9 NAFLD, and 5 infants completed the study. When FB- and BH-MRIs were compared, the correlation coefficients were $r=0.996$ and $p_c=0.994$. Mean ($\pm$ SE) H-PDFF and VAT were higher in the NAFLD vs CON ($21.9\% \pm 4.3\%$ vs $2.6 \pm 0.3\%$ and 876 ± 94 cm^3/m^2 vs 261 ± 18 cm^3/m^2 ($p < 0.001$)). H-PDFF was correlated with VAT ($r=0.86$, $p < 0.001$) (table 1). A H-PDFF threshold of 4.29% separates NAFLD from CON. For each unit increase in VAT-PDFF in the NAFLD group, H-PDFF increased by 2.64 ($r^2=0.54$, $p=0.02$). In infants, H-PDFF and VAT were $3.2\% \pm 0.8\%$ and 160 ± 64 cm^3/m^2 , respectively.

Conclusions FB-MRI is a novel tool to quantify body composition and liver disease in children. Research is warranted to determine if infants with increased VAT and hepatic fat are at risk for future NAFLD.

Abstract 243 Table 1 Correlation of H-PDFF for CON and NAFLD

	H-PDFF	
	r_s	P-value
Normalised VAT (cm^3/m^2)	0.86	<0.001
VAT-PDFF (%)	0.92	<0.001
BMI z-score	0.75	<0.001
Weight z-score	0.61	0.005
Waist-to-height ratio	0.79	<0.001
Alanine aminotransferase (U/L)	0.06	0.881

244 HEPATOCELLULAR CARCINOMA AND ASSOCIATED CLINICAL FEATURES IN LATINO AND CAUCASIAN PATIENTS IN A SINGLE CENTRE

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10.1136/jim-2017-000663.244

Purpose of study Hepatocellular carcinoma (HCC) is the most common form of liver cancer in adults and one of the most aggressive cancers with a five-year survival of approximately 16%. Racial/ethnic differences in HCC incidence have been observed with Hispanics showing the greatest increase over the past four decades, highlighting a concerning health disparity.

The goal of the present study was to determine the clinical features at the time of diagnosis of HCC in Latino compared to Caucasian patients.

Methods used We retrospectively screened a total of 559 charts of Latino and Caucasian patients who were evaluated at UC Davis Medical Centre between 01/01/2008 and 12/31/2014 with the diagnosis of HCC. Subjects were excluded from data analysis if the HCC diagnosis was not convincing (n=112) or if the ethnicity was not described or other than Latino or Caucasian (n=119). Statistical analyses were performed using SPSS Statistics, version 23. Differences between groups were assessed by two-tailed Student's T-test and by Fisher's Exact test.

Summary of results The mean age of HCC diagnosis was not significantly different between Latinos and Caucasians (63.4 ±11.7 vs 61±9.5 years, respectively). Latinos presented with higher BMI (30.2±6.6 vs 28±5.6; p=0.006). The rate of hypertension, diabetes, and hyperlipidemia was similar in the two groups. The aetiology of liver disease was more frequently alcohol drinking in Latinos (even though the difference did not reach statistical difference, p=0.08), whereas it was more frequently chronic hepatitis C in Caucasian patients (60% vs 73%; p=0.04). NASH was the associated diagnosis in 8.6% of Latinos and 4.7% of Caucasians (p=0.2). Interestingly, AFP levels at time of diagnosis was higher in Latino patients compared to Caucasians (9548.6±43645.5 vs 1761.7 ±6597.5 ng/mL, respectively; p=0.01) and this difference was evident only in male patients. Multifocal HCC was slightly more frequent in Latinos (p=0.06) but the two groups has similar cancerous vascular invasion.

Conclusions Latino and Caucasian patients with HCC present different profile of etiologies but cancer features appear to be more severe in Latinos. It is possible that Latinos require a more targeted approach to screening and treatment of HCC.

245 LATE PRESENTATION OF CYSTIC FIBROSIS AS PANCREATITIS IN AN ADOLESCENT

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10.1136/jim-2017-000663.245

Case report Cystic fibrosis (CF) is a genetic disorder of significant pulmonary disease that is usually diagnosed within the first few years of life from newborn screenings or clinical findings such as meconium ileus, failure to thrive, or chronic lung disease. Recent studies have identified gene mutations

that alter the cystic fibrosis transmembrane conductance regular (CFTR) protein responsible for the clinical findings of CF. Certain mutations that retain some function of the CFTR protein present with CF symptoms only when the CFTR protein fails to meet physiologic demands later in life. Further, each genetic mutation causes varying degrees of pathology that is specific to each tissue dependent on CFTR proteins. In this case, an adolescent male presented with chronic pancreatitis following a 3 year history of recurrent epigastric abdominal pain. He was found to have a positive sweat-chloride test diagnostic of CF, heterozygous *CFTR* mutations delta-F508/3849+10KbC >T, and normal pulmonary function test. The 3849+10KbC >T mutation is a splice mutation that results in fewer, but still functionally intact apical CFTR proteins, whereas the delta-F508 mutation results in loss of function of the CFTR protein. With preserved function, the 3849 +10KbC >T mutation is associated with later presentation of CF symptoms in life. This patient's unusual presentation of CF indicates that the CFTR protein may have different vulnerability to dysfunction in the pancreas than in the lungs. This case also demonstrates that the absence of pulmonary disease in childhood does not exclude the diagnosis of CF.

246 DOES LONG-TERM USE OF A PROTON PUMP INHIBITOR (PPI) LEAD TO OSTEOPENIA OR FRACTURES?

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Purpose of study Long-term use of PPIs to relieve symptoms related to gastroesophageal reflux is common. However, the side effects of long-term use of PPIs are unknown and need to be investigated. Our study provides a relevant, in depth review of current literature to determine if there is a correlation between PPI use and osteoporosis as well as fractures.

Methods used A thorough review of the literature was performed through PubMed, Google Scholar and review of reference lists of articles. We included research studies in which the subjects used at least one year of PPI. Studies that included paediatric patients and those that did not have a control group of non-PPI users were excluded.

Summary of results Our initial search produced 25 articles and of those, 9 studies met our inclusion criteria (see table 1 below). The definition of the subjects, controls, dosage of PPI, and outcomes were variable among the studies. Although the studies took other confounding variables, such as underlying illness, vitamin D and calcium intake into account, the subjects and controls did not have similar base-line characteristics in some of the case-control studies. The correlation between PPI use and osteopenia or fractures was more clear when PPI was used for more than 5–7 years.

Conclusions Our review suggests a link between osteopenia or fractures and PPI use of more than 5–7 years. However, the causality remains to be completely understood. Physicians should be aware of the potential risk of osteopenia and fractures with very long-term use of PPIs. Prospective randomised trials that outweigh the risk and benefits of PPIs are needed to better define guidelines for duration of PPI use.

Abstract 246 Table 1 Studies Summarizing the Association Between Long-term Use of PPIs and Osteopenia/Bone Fractures

Author, year	Study type	Age range	Duration of PPI use	Definition of subjects (total N) and % effected	Definition of control group (total N) and % effected	Odds ratio	P-value
Lewis JR, 2014	Longitudinal prospective cohort	Over 70 years	6 years	Osteopenic fractures in 17 of 120 (14.2%) of PPI Users	Osteopenic fractures in 77 of 905 (8.5%) of Non-PPI Users	1.78	0.046
Arj A, 2016	Cross-sectional	20–45 years	2 years	Femur Osteoporosis in 5 of 40 (12.5%) of PPI Users Lumbar Osteoporosis in 4 of 40 (10%) of PPI Users	Femur Osteoporosis in 0 of 40 (0%) of Non-PPI Users Lumbar Osteoporosis in 1 of 40 (2.5%) of Non-PPI Users		0.04 for femur 0.28 for lumbar
Targownik LE, 2008	National Database	Over 50 years	7 years	32 of 1830 (1.7%) with Osteopenic fractures used PPI more than 7 years	49 of 5482 (0.9%) matched controls with Osteopenic fractures did not use PPI	1.92	0.011
Yang YX, 2006	General Practice Research Database	Over 50 years	1 year 2 years 3 years 4 years	534 of 13 556 (3.9%) of PPI users had hip fractures	3228 of 1 35 386 (2.8%) of non-PPI users had hip fractures	1.4	<0.05
Ding J, 2014	Retrospective cohort	Over 65 years	Index date to fracture event	Incidence of fracture was 8.7% in 1604 PPI users	Incidence of fracture was 5% in 23 672 non-PPI users	1.28	0.003
Van der Hoorn, 2015	Longitudinal National Pharmaceutical Database	Over 75 years	7 years	827 of 2328 (36%) of PPI users used medication for osteopenia	550 of 2104 (26%) of non-PPI users used medication for osteopenia	1.29	0.006
Jacob L, 2016	Case-control	60–90 years	5 years	21.3% of 3092 of women with osteoporosis took PPIs	13.7% of 3092 women with osteoporosis did not take PPIs	1.62	0.001
Targownik LE, 2010	Manitoba Bone Mineral Density (BMD) Database	Over 60 years	5 years	110 patients had a BMD measurement after PPI use of 2–3 years	Same 110 patients had a baseline BMD measurement	Change in bone mineral density –0.08% lumbar –0.09% hip	>0.2
Targownik LE, 2017	PPI users identified in Manitoba Health Registry and surveyed	Over 60 years	5 years	52 PPI users with a Mean DXA score of 0.13 g/cm ²	52 non-PPI users with a Mean DXA score of 0.12 g/cm ²		>0.2

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MORPHOMETRIC AND CYTOLOGIC CHARACTERISATION OF ECTOPIC LYMPHOID TISSUE IN RESECTED BOWEL OF PATIENTS WITH DIVERTICULITIS, ULCERATIVE COLITIS, AND CROHN'S DISEASE

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10.1136/jim-2017-000663.247

Purpose of study Recent reports state that over 23 million Americans suffer from an autoimmune disorder. Implicated in many of these diseases is the development of Ectopic Lymphoid Tissues (ELT) in their pathogenesis. The present study aims to define the morphological and cytologic characteristics of ELTs in Crohn's disease, Ulcerative Colitis, and Diverticulitis with the goal improving treatment modalities and outcomes.

Methods used Resected bowel tissue was collected from 29 patients; 10 with Diverticulitis, 10 with Crohn's Disease and 9 with Ulcerative Colitis. Samples were formalin fixed, paraffin embedded, serially sectioned, and subsequently stained with immunohistochemical markers. Morphometric analysis was done using Olympus CellSens software and PerkinElmer Vectra 3.0 Automated Quantitative Pathology Imaging System. Cytologic analysis was done by isolating mRNA from FFPE tissues using the Ambion RecoverAll Kit and subsequent qPCR analysis. Statistical and Nearest Neighbour Analysis were performed using R Statistical Software.

Summary of results This study is still in progress. Preliminary results indicate that the number and size of B-cell aggregates differ between disease states as well as where in the bowel wall they organise. There is also a cross-sectional area cutoff

in which larger follicles develop into Tertiary Lymphoid Tissues (TLT) which have organised germinal centres. Cytological analysis suggests that there are distinct differences in chemokine profiles with Diverticulitis having a more T-cell driven profile, Ulcerative Colitis having a more B-cell driven profile. Fibrostenotic Crohn's samples showed lower expression of specific T (CCL19 and CCL21) and B-cell (CXCL12 and CXCL13) chemokines in comparison.

Conclusions Defining the composition of ELTs is an important first step in developing treatments for these disease states. The present study indicates that despite ELTs being implicated in all of these disease states their development and life cycles differ. This information should guide the development of future therapeutics and give more insight into how and why ELT development in various tissues.

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AN UNUSUAL PRESENTATION OF CROHN'S DISEASE; A SEVEN YEAR JOURNEY TO DIAGNOSIS

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10.1136/jim-2017-000663.248

Case report Crohn's disease is chronic inflammatory bowel disease (IBD) that presents 1/3 of the time in childhood. It may present abruptly or insidiously with abdominal pain, anal fissures, and hematochezia. It can also present with intermittent fevers, growth failure, malnutrition, and pubertal delay. Paediatricians must have a high index of suspicion given its potential impact. Below we present an unusual case.

The patient presented at age 5 with aphthous ulcers and a 10 day history of intermittent fevers up to 104 degrees. He had experienced recurrent episodes of fevers and mouth sores every 4–6 weeks since age 3. He was worked up for Kawasaki's, Bechet's, and periodic fever adenitis pharyngitis aphthous ulcer syndrome (PFAPA) and was initially diagnosed with PFAPA. He underwent adenoidectomy and tonsillectomy and was symptom free for one year. His symptoms recurred and he was referred to paediatric rheumatology. Review of symptoms revealed frequent diarrhoea, and a work up for celiac disease and IBD began.

A CBC, CMP, ESR, CRP, celiac panel, and IBD diagnostic panel were sent. His lab work was notable for an elevated CRP of 31.2 mg/L and ESR of 21 mm/hr. He was referred to paediatric gastroenterology. At that point his physical exam was unremarkable. He underwent EGD and colonoscopy with biopsies, both of which were normal. He was diagnosed with constipation. Rheumatology treated him with Azathioprine and intermittent corticosteroids whenever aphthous ulcers recurred.

By age 10, the patient developed perianal ulcers and crampy periumbilical pain. His physical exam was now positive for periumbilical tenderness. Gastroenterology performed an abdominal MR enterography, faecal calprotectin, and small bowel video capsule study which were normal. A Prometheus IBD diagnostic panel revealed positive anti-CBir1, anti-A4-Fla2, and anti-FLAX IgG. He was subsequently diagnosed with Crohn's disease, perianal phenotype, and started on Adalimumab. He has since done well with no recurrence of aphthous ulcers or perianal disease. In diagnostically challenging cases it is crucial to keep inflammatory bowel disease as a differential diagnosis and use new serologic testing like the Prometheus IBD panel to assist diagnosis given the impact it may have on a child.

249 QUALITY IMPROVEMENT: THE NUTRITIONAL AND GROWTH STATUS OF INFLAMMATORY BOWEL DISEASE PATIENTS AT UNIV. OF NEW MEXICO

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10.1136/jim-2017-000663.249

Purpose of study Over one million people suffer from Inflammatory Bowel Disease (IBD) in the United States. Impaired growth and nutritional status are of significant concern in IBD and can be seen in 65%–85% of paediatric patients with Crohn's disease. Impaired growth and nutritional status can have significant consequences, including effects on development and cognitive function. ImproveCareNow (ICN) is a network of over 90 centres working together to provide optimal care for children with IBD. ICN has improved remission rates through collaborative research and data sharing. We aimed to assess two of the ICN clinical measures, growth and nutrition in patients enrolled in ICN at University of New Mexico. We assessed patients' growth and nutrition status, and identified whether the ICN nutrition and growth algorithm guidelines were adequately followed.

Methods used We performed a retrospective chart review of paediatric IBD patients at UNM in the ICN database. We identified patients classified as having unsatisfactory nutritional and growth status as of June 2017. Patient data was analysed and compared to ICN targets using data provided by the ICN Network and collected by Centres participating in the ICN network.

Summary of results The ICN target for satisfactory growth and nutrition is 90% of patients. As of June 2017, 72% of our population had satisfactory nutritional status and 83% had satisfactory growth. Yearly visits with a registered dietician (RD) are recommended for all IBD patients and more frequently in patients with unsatisfactory nutritional and growth status. Of the patients with unsatisfactory nutritional and growth status 22% and 0% visited a RD in the past year, respectively.

Conclusions UNM was below the ICN targets for satisfactory growth and nutritional status. As UNM joined ICN just over a year ago, data is still insufficient to know if our patient population differs from that of the collaborate (which may explain some of the differences seen in our study). The area with the most potential for improvement is more frequent RD visits and follow up appointments. We purposed an electronic medical record template for IBD patient visits to include specific ICN algorithm recommendations as prompts for providers, which will help identify those in need of additional interventions (RD assessment or increased visit frequency).

Genetics

Concurrent session

Friday, January 27, 2017

8:00 AM – 10:00 AM

250 A NOVEL AUTOSOMAL DOMINANT SYNDROME RESULTING FROM VARIANTS IN *CDC42*

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10.1136/jim-2017-000663.250

Purpose of study We report on a patient with a heterozygous variant in *CDC42* identified through whole exome sequencing. *CDC42* encodes a GTPase and is a member of the Rho signalling family, which is part of the larger Ras cascade. The Rho signalling pathway regulates a variety of cellular processes including transcription, trafficking and cell cycle progression. Mouse models have demonstrated that *CDC42* GTPase activity is critical for myeloid and erythroid cell development. *CDC42* knockout mice had abnormal erythropoiesis, decreased activity of erythroid progenitor cells and infiltration of various organs by myeloid cells. The *CDC42* protein is ubiquitously expressed in the human body. *CDC42* RNA expression is highest in bone marrow, spleen, skin, placenta and smooth muscle. The purpose of this article is to document a novel gene associated with hematologic and immunologic sequelae and to define the associated phenotype.

Methods used Whole exome sequencing performed. Collection of phenotypic data from the clinical chart. Use of GeneMatcher to identify several additional providers with patients that had heterozygous variants in *CDC42*.

Summary of results An 11 month old, former 32 week gestation female was evaluated for history of hydrops, cholestasis and thrombocytopenia as well as persistent hepatosplenomegaly and anaemia with mild developmental delay. She also had intermittent erythematous rashes and swelling over various parts of the body. A *de novo*, heterozygous, likely pathogenic variant in *CDC42* c.563G>A(p.C188Y) was detected on whole exome sequencing. We identified several additional patients with similar phenotypes through GeneMatcher.

Conclusions These results support the possibility of a novel autosomal dominant syndrome resulting from variants in *CDC42*. The overlapping phenotypes of our patient with those identified through GeneMatcher and with knockout mouse models suggests pathogenicity. Future functional studies and identification of additional cases will help confirm pathogenicity and further clarify the phenotype.

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EXPANDING THE GENETIC AND CLINICAL SPECTRUM OF THE *NONO*-ASSOCIATED X-LINKED INTELLECTUAL DISABILITY SYNDROME WITH LEFT VENTRICULAR NON-COMPACTION

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10.1136/jim-2017-000663.251

Purpose of study A two-year-old boy presented to the University of Utah's Penelope Undiagnosed Disease Program with global developmental delay, congenital heart disease consisting of dilated cardiomyopathy with left ventricular non-compaction and Ebstein's anomaly, strabismus, undescended testes, and mixed sleep apnea. He was small (length and weight <1%) with preserved head size (85%). On exam, we noted a triangular shape of the face with wide-spaced eyes, downslanting palpebral fissures, and a thin vermilion of the upper lip. Brain MRI showed a thick corpus callosum and a mild Chiari I malformation.

Methods used Exome sequencing was performed, as well as follow-up RNA studies and family segregation analysis, to aid in diagnosis.

Summary of results Exome sequencing identified a maternally-inherited small intronic deletion in the *NONO* gene. This X-linked gene encodes a nuclear protein involved in RNA metabolism. Loss-of-function variants have been associated with a syndromic form of intellectual disability (Mircsof et al. 2015) and with non-compaction cardiomyopathy (Reinstein et al. 2016, Scott et al. 2017). Notwithstanding the clinical overlap with the few reported cases, without functional studies this intronic *NONO* deletion was initially classified as a variant of uncertain significance. However, follow up splicing studies demonstrated intron readthrough and the use of an alternative donor 13 bases into the intron, causing a frameshift and creating a transcript susceptible to nonsense-mediated decay. Also, family segregation studies showed that the variant occurred *de novo* in the boy's unaffected mother.

Conclusions Based on these findings this novel *NONO* variant was reclassified as pathogenic. This eighth known case expands and further delineates the neurological and cardiac phenotypes of this rare X-linked condition.

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GERMLINE TRANSMISSION OF PATHOGENIC BRAF: EXPANDING THE CLINICAL PHENOTYPE OF CFC SYNDROME

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Purpose of study Cardio-facio-cutaneous syndrome (CFC) is one of the RASopathies and is caused by alteration of activity

of the Ras/MAPK pathway due to heterozygous *de novo* germline mutations in protein kinases BRAF, MEK1 or MEK2. The gene KRAS has been reported in both CFC and Noonan syndrome so its role in CFC remains unclear. CFC is a multiple congenital anomaly disorder in which individuals typically have characteristic dysmorphic features, cardiac defects, ectodermal anomalies and developmental delay. The mutations for CFC are typically considered *de novo* because vertical transmission of a MEK2 mutation has been reported in one CFC family. Vertical transmission of BRAF has never been reported. **Methods used** We report on a 3 year old male with clinical features consistent with the diagnosis of a RASopathy. He presented with history of pulmonary valve stenosis, cryptorchidism, cutaneous findings and developmental delay. The proband was sequenced using a commercial RASopathy gene panel and biochemical analysis was assessed by Western blot.

Summary of results Sequencing revealed a heterozygous variant in *BRAF* (c.1390 G>C; p.G464R) consistent with CFC. *In silico* analyses predicted the variant as 'probably damaging'. Functional analysis of this mutation has never been reported. To corroborate the functional alteration of the mutant, transient transfection of HEK293T cells with subsequent Western analysis was used and demonstrated increased protein kinase activity. Additionally, the proband's mother was noted to have similar cutaneous findings as her child, as well as short stature and mild learning issues. Targeted testing in the mother determined that she also carried the same BRAF variant. During the time of the mother's workup, she became pregnant. Post-natal testing was positive for the BRAF p.G464R missense mutation.

Conclusions This is the first identified vertically transmitted functional CFC BRAF mutation reported and expands our understanding of germline mutations and their transmission within the Ras/MAPK pathway. Additionally, our findings underscore the importance of a thorough genetic evaluation of family members and that activating mutant proteins within the MAPK cascade mediated by Raf are compatible with human reproduction.

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ISOLATED SULFITE OXIDASE DEFICIENCY IN A 2 YEAR-OLD MALE, A DIAGNOSIS MISSED IN THE NEONATAL PERIOD

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10.1136/jim-2017-000663.253

Purpose of the study Sulfite oxidase catalyses the terminal reaction of the oxidative degradation of the sulfur-containing amino acids cysteine and methionine. Deficiency of sulfite oxidase can occur via either a defect in the synthesis of the molybdenum cofactor, which also affects xanthine dehydrogenase and aldehyde oxidase; or a deficiency of sulfite oxidase enzyme activity alone. Early identification of this condition allows the family to receive the appropriate support and genetic counselling.

Methods used We report a patient who previously presented with neonatal encephalopathy and spasticity. He then presented with apneic episodes at age 2 that required intubation. He had significant delays. Physical exam identified microcephaly and hypotonia. Brain MRI in the neonatal period showed marked signal and diffusion abnormality in the white

matter suggestive of sulfite oxidase deficiency. The patient had no follow up until he was re-admitted to our hospital.

Summary of results Evaluation in infancy showed to a mildly elevated S-sulfocysteine in infancy, done by High Performance Liquid Chromatography (HPLC), but this was reported not to reach the threshold for disease.

Sulfite oxidase deficiency was again suggested by brain MRI at age two. Laboratories in his last admission identified elevated plasma lactate, low total plasma homocysteine, normal urine purines and normal plasma uric acids. Plasma Cysteine was low. Urine S-sulfocysteine level was performed at a different laboratory using tandem mass spectrometry (MS/MS) and was markedly elevated. SUOX gene testing showed a homozygous pathogenic variant c.363dupG, predicting (p. Pro122Alafs*29). The brain MRI showed microcephaly, worsening global cerebral volume loss, encephalomalacia, and increased involvement of the basal ganglia compared to prior imaging.

This case represents a delayed diagnosis of an isolated sulfite oxidase deficiency 2 years after the initial presentation. Different lab methods had resulted in different diagnostic threshold. The patient's parents withdrew support leading to his death shortly after he was diagnosed due to the poor prognosis of this disease.

254 NON-EPILEPTIFORM MOVEMENTS AND 5Q31.3 MICRODELETION

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10.1136/jim-2017-000663.254

Case report The 5q31.3 microdeletion including the gene *PURA* causes a syndrome of severe developmental delay and seizures. Eleven cases of del5q31.3 have been described. Most reports are of patients identified in childhood with developmental delay. Here we describe the neonatal presentation which is unique and seems to be specific for this diagnosis. We propose del5q31.3 is a diagnosis to consider when a neonate displays abnormal, non-epileptiform movements in association with gross hypotonia.

Our patient was born at term after a normal pregnancy, the first child to unrelated, healthy parents. He was noted to have central hypotonia and quickly developed irregular breathing and abnormal facial and extremity movements, concerning for seizure activity. The movements were; myoclonic/dyskinetic in nature, isolated facial, single extremity or more generalised, more frequent when awake and with manipulation but occurred when the patient was resting comfortably. Neither bedside nor 12 channel EEG exams showed any evidence of seizure activity. His hypotonia and abnormal movements continued despite antibiotic and antiepileptic treatments. He also had recurrent apnea, central or reflux-related. A large etiologic evaluation was undertaken and he was found to have 5q31.2q31.3 microdeletion (494 KB interstitial deletion) including *PURA*, *NRG2* and *PFDN1* genes. MRI showed only mild parenchymal volume loss. The remainder of his studies were unremarkable.

The del5q31.3 has shown a highly consistent phenotype to date. The most notable neonatal features are hypotonia, apnea, infantile feeding difficulties, and abnormal non-epileptic movements. Later in life, children can develop seizures and demonstrate severe developmental delay. Our patient's

microdeletion included the *PURA* gene, supporting *PURA* as the causative gene in del5q31.3. Presentation of del5q31.3 and *PURA* associated disorders in neonates is unique among disorders associated with neurocognitive dysfunction and seizures. The majority of patients are reported to have non-epileptic movements, many specifically in the newborn period. Prior reports do not emphasise this early presentation. We believe that if *PURA* or del5q31.3 is recognised as a neonatal movement disorder, earlier identification may be possible. This in turn could lead to appropriate interventions and avoidance of unnecessary studies and treatments.

255 NOVEL PATHOGENIC VARIANTS AND CLINICAL SPECTRUM OF A DIVERSE RETINOBLASTOMA COHORT

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10.1136/jim-2017-000663.255

Purpose of study To determine the genetic and clinical spectrum of retinoblastoma patients evaluated at Children's Healthcare of Atlanta (CHOA) and Emory Eye Clinic (EEC).

Methods used This was a retrospective cohort study of all individuals with a clinical diagnosis of retinoblastoma evaluated from January 2010 to December 2015. We evaluated patient demographics, clinical diagnosis methods, MRI studies, identification of additional tumours/metastasis, and, results of germline and/or tumour genetic testing. Additionally, we report on family history of retinoblastoma, or other tumours and on whether targeted genetic testing for retinoblastoma was utilised by at-risk family members when a germline *RB1* mutation was identified.

Summary of results We identified 152 individuals using the ICD 9 code 190.5, for malignant neoplasm of retina, of which 127 were confirmed to have a clinical diagnosis of retinoblastoma upon manual review. Our cohort included 68 (53%) Caucasians, 48 (38%) African-Americans, 2 (<2%) Asians, and, 9 (7%) others. Sixty-four (51%) individuals had bilateral/trilateral retinoblastoma and 63 (49%) had unilateral retinoblastoma. Germline testing was performed in 84 (66%) individuals, of whom 33/37 (89%) bilateral/trilateral and 12/47 (25%) unilateral RB individuals had positive germline testing. We identified 11 novel mutations. Seventeen (13%) individuals had a family history of RB and 14 (11%) probands reported other malignancies in their family. Targeted genetic testing was reported in 5 at-risk relatives.

Conclusions The demography of our RB cohort is unique with larger number of African American population. While genetic testing of affected individuals is performed in the majority of RB individuals, extension of targeted genetic testing among at-risk individuals is under-utilised. Future studies to evaluate whether a genetic evaluation and/or involving genetic counsellor would improve patient and family member uptake of genetic testing would be beneficial.

256 THYMIDINE KINASE 2-RELATED MITOCHONDRIAL DEPLETION SYNDROME IN A PAIR OF SIBLINGS – A DIAGNOSTIC ODYSSEY LEADING TO POSSIBLE TREATMENT

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10.1136/jim-2017-000663.256

Case report Diagnosing mitochondrial disease is quite challenging because there can be a wide and varied degree of organ system involvement, even among affected individuals within the same family. Two siblings are presented who were ultimately determined to have TK2-related mitochondrial depletion syndrome.

The proband was 11 years old when she first presented to the Genetics Clinic for poor ability to gain weight and gastroparesis. Her cognitive abilities were normal, but there were mild gross motor concerns (poorer performance in sports, climbs stairs slowly). A basic inborn error of metabolism work-up was normal (including lactate), SNP chromosome microarray revealed a likely benign CNV but also remote consanguinity, and CPK was elevated. Muscle biopsy showed non-specific findings on pathology as well as respiratory chain enzymatic analyses.

The proband's brother is 2.5 years younger in age, and has a more prominent myopathic phenotype. However, in contrast to his sister, he is without GI or weight gain concerns. Although he walked on time (14 months old), his hypotonia became more apparent through childhood. As a preteen, he continues with PT, still falls on occasion, and needs to climb stairs while holding on. His initial work-up was similarly negative, except for his CPK being mildly elevated.

Clinical whole exome sequencing uncovered homozygous likely pathogenic variants in thymidine kinase 2 (TK2) for both of the siblings. TK2 is an initial step in the generation of intramitochondrial nucleotides used in mitochondrial DNA replication. Pathogenic variants in a number of genes within these pathways result in mitochondrial DNA depletion syndromes, although in some instances (such as with TK2 mutations), quantification of mtDNA content can be normal. Studies in mice have been published showing clinical improvement with oral therapy aimed at bypassing the blocked synthesis step with exogenously administered nucleosides. Anecdotal evidence indicates a similar response in humans, and these siblings aim to enrol in pre-clinical trials.

These two siblings illustrate the variability of clinical phenotypes in mitochondrial disease, but also highlight a less common (but arguably more gratifying) benefit of arriving at a genetic diagnosis: a treatment for the underlying condition may be available.

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CHARACTERISATION OF CUTANEOUS MOSAICISM USING DISTINCT GENOMIC TECHNOLOGIES: *GNAQ* AND RECOGNITION OF A MOSAIC RASOPATHY

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10.1136/jim-2017-000663.257

Purpose of study Mosaicism is recognised more often on the skin because phenotypic variation is more readily identified compared to other organs. In clinical practice, one of the best known forms of mosaicism is that of cancer. However, the difference between genetic variations causing heterozygous postzygotic changes and those causing loss of heterozygosity, for example, is challenging to discern without molecular testing. Genomic technologies, including next generation sequencing, have improved our ability to assess genomic variation with greater resolution. Here we utilise genomic technologies in the evaluation of three patients with cutaneous mosaicism

and in the characterisation of a distinct *GNAQ*-RASopathy disease process.

Methods used Patient 1 had whole exome sequencing on blood and capture-based next generation sequencing (NGS) of 500 cancer-causing genes (UCSF 500) on skin, buccal, and blood samples. Patients 2 and 3 had select analysis of epilepsy- or RAS-related genes on blood and/or skin samples using NGS. Chromosomal analysis was done on one skin sample. SNP microarray was also performed in two of three patients.

Summary of results We first describe a patient who presented with signs of phakomatosis pigmentovascularis, type 2, but also with seizures and brain malformation. Lesional skin biopsy, buccal cells, and peripheral blood were tested. A p. R183Q *GNAQ* variant was identified at 5% and 3% variant allele frequencies in skin and buccal samples respectively, confirming mosaicism. In cases of extensive phakomatosis pigmentovascularis, activating mutations in *GNAQ* have been identified. However, other systemic malformations are unusual. *GNAQ* functions in the RAS pathway. Exome sequencing revealed potential candidates for additional phenotype exacerbation. Another patient presented with extensive unilateral pigmented skin involvement, likely due to RASopathy gene alteration, and mosaicism studies were performed for a third.

Conclusions We have found a mosaic *GNAQ* alteration in a unique RASopathy condition. The recognition of cutaneous mosaic RASopathies and the utility in diagnostics is growing rapidly. Advances in genomic technology have improved our ability to detect and characterise diverse molecular genetic types of mosaicism with greater sensitivity.

Neonatology – pulmonary III

Concurrent session

Friday, January 27, 2017

8:00 AM – 10:00 AM

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HMGB1 SIGNALLING IS ATTENUATED IN ENDOTOXEMIC NEONATAL MICE VIA A STAT1-MEDIATED MECHANISM

S McKenna*, J Sandoval, T Burey, J Gonzalez, B Butler, CJ Wright. *University of Colorado, Aurora, CO*

10.1136/jim-2017-000663.258

Purpose of study Sepsis is a major cause of neonatal morbidity and mortality, but the mechanisms linking neonatal susceptibility to infection and mortality are unclear. Elevated serum levels of the dual-function cytokine HMGB1, a late mediator of septic shock that signals through the Receptor for Advanced Glycation End Products (RAGE), are associated with adult mortality during sepsis, but recent studies have shown that absence of HMGB1 signalling in the context of endotoxemia is also detrimental to survival. STAT1-mediated HMGB1 acetylation is essential for HMGB1 nuclear release in the context of inflammatory stress; however, the mechanisms by which STAT1-mediated HMGB1 nuclear release might contribute to neonatal susceptibility to endotoxemia are unknown. The objective of this study was to determine the mechanisms regulating HMGB1 signalling in endotoxemic neonatal mice.

Methods used To induce endotoxemia, neonatal (PN0) and adult (8–10 wk) mice were exposed to LPS (5 mg/kg, IP). Expression of the STAT1 agonist IFN β was assessed by qPCR. Circulating IFN β was measured by serum ELISA, and pulmonary STAT1 signalling assessed by Western Blot. Expression of RAGE target genes was assessed by qPCR. To interrogate the mechanisms of STAT1-mediated HMGB1 nuclear release, RAW 264.7 cells were exposed to LPS (1 μ g/ml) or IFN β (100–1000 U/ml) and STAT1 signalling and HMGB1 expression were assessed by Western blot.

Summary of results In contrast to adult endotoxemic mice, expression of IFN β was attenuated in neonatal mice. This was associated with significantly reduced STAT1 signalling in neonatal pulmonary cytosolic extracts ($p < 0.05$), and significantly reduced neonatal pulmonary expression of RAGE-dependent target genes TNF α , MCP1, and MIP1 α ($p < 0.05$) compared to the adult. Thus, the HMGB1/RAGE signalling axis is attenuated in the neonatal lung via a STAT1-dependent mechanism.

Conclusions Multiple factors result in impaired neonatal HMGB1/RAGE signalling following systemic inflammatory stress. In adults, exaggerated HMGB1 release is late-mediator of mortality associated with sepsis. In contrast, attenuated HMGB1/RAGE signalling complicates neonatal endotoxemia. These results suggest that targeting nuclear release of HMGB1 may be beneficial during neonatal sepsis.

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DIFFERENTIAL INFLAMMATORY RESPONSES IN FETAL MACROPHAGE POPULATIONS

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10.1136/jim-2017-000663.259

Purpose of study Inflammation and injury play key roles in complications of prematurity. Macrophages are crucial response cells in fetal and neonatal innate immune systems. Developing tissues contain macrophage populations derived from both the yolk sac and fetal liver. Our previous work implicated cytokine production by macrophages in lung injury and abnormal lung development. The relative contributions of these macrophage populations to fetal and neonatal inflammation is unclear. This project tests the hypothesis that fetal liver and yolk sac derived macrophages have distinct inflammatory properties.

Methods used Macrophage populations from E15 mouse lung, liver, and brain were sorted by FACS based on CD11b and F4/80 expression. Sorted cells were treated with inflammatory agonists (LPS, PAM3, FLSL-1, Poly I:C HMW, Poly I:C LMW, HLKM, ODN, Flagellin, TNF, IFN, and IL-13). For comparison, alveolar macrophages isolated from adult mice via bronchial alveolar lavage were treated with LPS, Poly I:C LMW, IFN, PAM3, TNF, and Imiquimod. After four hours of treatment, relative expression of mRNA was measured by real time PCR. Protein release into the media was measured by ELISA.

Summary of results CD11b^{HI} fetal liver macrophages (FLM) isolated from either E15 liver or lung expressed and released significantly higher levels of IL-1 β and IL-6 compared to F4/80^{HI} yolk sac derived macrophages (YSM). Flow cytometry showed increased proIL-1 β and TNF in FLM after LPS treatment. FLM from E15 lung and liver express higher levels of the inflammatory regulator *Socs3* compared to YSM. However,

expression of other inflammatory mediators and innate immune signalling genes was comparable between macrophage populations. Macrophages from E15 liver treated with several inflammatory agonists consistently expressed higher IL-1 β in FLM compared to YSM. Therefore, FLM appear to express and release increased IL-1 β in response to multiple innate immune stimuli.

Conclusions In both developing lung and liver, FLM express higher levels of IL-1 β and TNF in response to innate immune activation when compared to YSM. Understanding the relative roles of these distinct populations in tissue injury and repair could have important implications in neonatal disease.

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THE ROLE OF IKK ϵ /IRF3 IN MEDIATING CHRONIC PULMONARY INFLAMMATION FOLLOWING EXPOSURE TO SYSTEMIC INFLAMMATORY STRESS IN THE PERINATAL PERIOD

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10.1136/jim-2017-000663.260

Purpose of study Sustained expression of pro-inflammatory mediators has been identified as a risk factor for developing bronchopulmonary dysplasia (BPD). However, the mechanisms underlying chronic inflammation following neonatal insult are unknown. Following the initial wave of the innate immune response to inflammatory stress, the kinase IKK ϵ activates the TF IRF3 initiating a late-phase type I interferon and pro-inflammatory cytokine response. It is unknown whether this late phase response contributes to chronic inflammation in the neonatal lung.

Methods used Neonatal (P0) and adult ICR were exposed to LPS (5 mg/kg IP, 5–7/time point) for 6/12/24 hours. Pulmonary protein and mRNA was isolated and IKK ϵ /IRF3 activation was assessed by Western blot. IKK ϵ /IRF3 gene expression as well as the expression of their target genes was assessed by RT-qPCR.

Summary of results Endotoxemia significantly increased IKK ϵ expression in adult mice at 6/12/24 hours ($p < 0.05$). Notably, endotoxemia resulted in significant ($p < 0.05$) pulmonary IKK ϵ induction in neonatal mice, but levels were significantly attenuated compared to similarly exposed adults ($p < 0.05$). Consistent with attenuated IKK ϵ expression, phosphorylated-IRF3 was significantly lower in neonatal mice when compared to adult mice. Despite attenuated IKK ϵ /p-IRF3 activity, IRF3 dependent gene expression was not uniformly attenuated in the neonatal lung. Only neonatal IFN β was significantly attenuated; whereas induction of IRG1 was similar in neonates and adults. In contrast, expression of RANTES, IP10, IFIT1 was significantly increased ($p < 0.05$) in the neonate compared to adult.

Conclusions Consistent with our hypothesis, we found LPS-induced IKK ϵ /IRF3 activation and target gene expression in the neonatal lung. Altogether, these findings may provide clues as to the role of critical aspects of the innate immune response may play a critical role in development of neonatal lung injury. Future work will investigate developmentally regulated mechanisms dictating developmentally-regulated expression of IKK ϵ /IRF3 target genes following exposure to systemic inflammatory stress.

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GENOMIC ASSESSMENT REVEALS MARKED DIFFERENCES IN THE INFLAMMATORY RESPONSE OF MONONUCLEAR PHAGOCYTES IN THE LUNG

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10.1136/jim-2017-000663.261

Purpose of study While a division of labour during inflammation has been proposed for lung mononuclear phagocytes (MP), the phenotypic and functional characteristics of MP subsets are poorly characterised. Therefore, our goal was to determine the transcriptomic profile of alveolar macrophages (AM), interstitial macrophages (IM), and monocytes in the mouse lung at different time points after intraperitoneal administration of lipopolysaccharide (LPS).

Methods used C57BL/6J mice were intraperitoneally injected with LPS and lungs were harvested at 0 hour, 2 hour, 6 hour and 22 hour after the challenge. MP subsets were sorted by fluorescence-activated cell sorting. Gene expression at the four time points was determined by RNA-sequencing. Open regions of chromatin were determined using the transposase-accessible-chromatin-sequencing assay. Data were analysed with HOMER.

Summary of results Lung MP showed significant differences in gene expression after *in vivo* LPS stimulation with hundreds of mRNA transcripts selectively increased or decreased in only one subset at any given time point. Gene ontology annotation of the uniquely expressed genes revealed a pronounced enrichment for inflammatory response and mitotic cell process genes in IM and monocytes. AM showed a significantly dampened immune response with enrichment for genes involved in cell migration and lipid metabolism. Each MP subset showed a unique temporal pattern of gene expression. IM and monocytes showed a rapid up regulation of inflammatory genes with peak expression at 2 hour. AM showed a slower activation with expression of cell migration and wound healing genes at 22 hour. Motif enrichment analysis of open chromatin regions identified several MP subset specific transcription factor binding motifs.

Conclusions Transcriptomic profiling of lung MP collected over the course of the inflammatory response revealed a marked functional diversity among subsets. Signature genes identified IM and monocytes as the main drivers of the inflammatory response. AM had a significantly lower expression of inflammatory genes suggesting transcriptional mechanisms that prevent them from mounting an excessive immune response. Importantly, AM were enriched in wound healing genes in the resolution phase. These results have important implications for the design of targeted therapy.

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SEX-SPECIFIC PKC ISOFORM EXPRESSION MECHANISTICALLY EXPLAINS THE SEX-SPECIFIC PERINATAL SMOKE INDUCED AIRWAY HYPER-RESPONSIVENESS

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10.1136/jim-2017-000663.262

Purpose of study Maternal smoking during pregnancy results in detrimental long-term effects on lung growth and function, including an increased predisposition to asthma in the exposed

offspring. In a well-established rat model of nicotine-induced lung phenotype, we have previously demonstrated sex-specific structural, molecular and functional changes in tracheas, with selective involvement in males; however, the molecular mechanisms underlying these differential sex-specific effects are unknown. Since Protein Kinase C (PKC) signalling is a key determinant of airway development and contractility, we hypothesised that differential PKC isoform expression pattern, and activation accounts for the differential perinatal nicotine-induced airway phenotype in males and females.

Methods used Pregnant Sprague Dawley rat dams received either placebo, nicotine 1 mg/kg, or nicotine +rosiglitazone (RGZ) 3 mg/kg, a PPAR γ agonist, once daily from embryonic day 6 until postnatal day (PND) 21 when pups were sacrificed. Using qRT-PCR and Western blotting, specific PKC isoform expression in trachea was determined in a sex-specific manner. In addition, male and female PND21 tracheal smooth muscle cells (TSMCs) were treated with nicotine 1×10^{-6} M alone, or in combination with specific PKC isoform antagonists.

Summary of results Although there was no significant difference in the expression of typical and conventional PKC isoforms in the male and female tracheas, the expression of novel PKC isoforms was significantly increased in nicotine-exposed males, but not in females. In addition, cultured TSMCs demonstrated increased activation in novel PKC isoforms exclusively in males. RGZ treatment and pre-treatment with specific PKC-isoform antagonists blocked nicotine-induced increase in novel PKC-isoform mRNA and protein levels, as well as its downstream airway contractility targets.

Conclusions Our data suggest sex-specific PKC isoform expression as the mechanistic basis underlying the differential perinatal nicotine-induced airway phenotype in males and females, allowing us to speculate targeting specific PKC isoforms as a novel therapeutic strategy for differentially treating perinatal smoke-induced asthma in males and females.

Neonatology – general III

Concurrent session

Friday, January 26, 2018

8:00 AM – 10:00 AM

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COMPOSITIONAL ANALYSIS OF DONOR HUMAN MILK

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10.1136/jim-2017-000663.263

Purpose of study In the event exclusive breastfeeding is not possible, pasteurised and pooled donor human milk (DHM) is the ideal alternative. The majority of DHM is prioritised for premature infants, as it improves health outcomes in this vulnerable population with elevated calorie, micronutrient, and immune protection needs. Given that human milk is largely donated later in lactation (>3 mo. post-partum), it alone may not meet premature infants' calorie and zinc needs, as zinc dramatically decreases in human milk over the course of lactation. Additionally, HM insulin is related to maternal insulin sensitivity, meaning insulin concentrations in DHM are likely

to vary. This study aims to confirm the caloric density and quantify the zinc concentration of DHM, as well as to assess the variability in insulin concentrations.

Methods used Samples (n=128) of DHM were obtained from Mothers' Milk Bank (MMB) (Arvada, CO), where caloric density was measured via ultrasonography (Scope Electric analyzer). Macronutrient and caloric profile of DHM were reassessed via infrared spectroscopy (Miris Human Milk Analyzer (HMA)). Zinc concentration was measured via atomic absorption spectroscopy in 110 term samples. Insulin concentrations were measured in both pre- and post-pasteurised samples by chemiluminescent immunoassay in 52 samples.

Summary of results Mean calorie content was 17.3 cal/oz by the HMA, compared to 18.8 cal/oz according to the MMB ($p<0.0001$). Of the samples classified by the MMB as 'high calorie' (≥ 22 cal/oz), only 6.7% were confirmed ≥ 22 . Mean Zn concentration was 1.44 $\mu\text{g/mL}$, with considerable variability (0.34–4.31 $\mu\text{g/mL}$). Insulin concentrations decreased by 13.6% post-pasteurisation ($p<0.0001$), and ranged between 3 and 21 $\mu\text{IU/mL}$.

Conclusions These findings suggest the caloric density of DHM may be overestimated by ultrasonographic technique. Zinc concentrations of term DHM were representative of HM produced at 4 months post-partum, which supports the importance of routine zinc fortification for premature infants receiving DHM. These data confirm that pasteurisation diminishes hormone concentrations in HM, but highlight the inter-pool variability in insulin content to which a recipient infant may be exposed.

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DOES CHOICE OF HUMAN MILK FORTIFIERS AFFECT FEEDING TOLERANCE AND NUTRITION IN PREMATURE INFANTS?

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10.1136/jim-2017-000663.264

Purpose of study Compare feeding tolerance and nutritional outcomes of preterm infants whose human milk diet was fortified with acidified versus non-acidified Human Milk Fortifier (HMF).

Methods used This was an unblinded, randomised controlled, single-centre study of preterm infants born at <35 weeks gestation or <1800 grams who were fed only human milk fortified with either acidified or non-acidified HMF. Feeding intolerance, and laboratory data including serum protein and albumin, pH and bicarbonate were analysed. Feeding intolerance was defined as the point at which feeds were held due to abdominal distention, excessive or bilious gastric residuals, emesis, diarrhoea or bloody stool.

Summary of results 80 infants were enrolled in the study; 40 received acidified HMF and 40 received non-acidified HMF added when enteral feeds were at 35% of goal per unit feeding protocol. There were no statistically significant differences between the groups in birth weight or gestational age, days of mechanical ventilation, incidence of NEC or sepsis, length of stay or feeding intolerance. Infants who received acidified HMF vs non-acidified had higher total serum albumin at 7 days ($\mu \pm \text{SD}$, 3.39 ± 0.34 vs 3.17 ± 0.33 , $p=0.009$) and 14 days (3.39 ± 0.38 vs 3.15 ± 0.33 , $p=0.014$). They also had higher total serum protein at 14 days (5 ± 0.61 vs 4.52 ± 0.56 ,

$p=0.001$) and 21 days (4.87 ± 0.61 vs 4.56 ± 0.47 , $p=0.041$). Serum bicarbonate levels were lower in the acidified HMF group at 7, 14 and 21 days after fortification (22.15 ± 6.03 vs 25.34 ± 2.64 , $p=0.004$; 23.26 ± 3.75 vs 24.97 ± 2.68 , $p=0.04$; and 23.5 ± 4.64 vs 25.74 ± 2.6 , $p=0.03$ respectively).

Conclusions No statistical significance in rates of feeding intolerance were found between preterm infants fed a human milk diet fortified with acidified HMF compared to fortification with non-acidified HMF. Those receiving acidified HMF had higher total serum protein and albumin levels and lower bicarbonate levels with statistical significance, but uncertain clinical significance, between groups.

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EVALUATION OF A NUTRITION PROTOCOL ON INFECTIOUS AND GROWTH OUTCOMES

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10.1136/jim-2017-000663.265

Purpose of study Standardised feeding protocols can improve infectious outcomes like necrotizing enterocolitis (NEC). An internal review revealed a non-uniform approach to the nutrition of preterm infants and high NEC rates. Donor human milk (DHM) was not available. We hypothesised that a nutrition bundle quality improvement (QI) initiative would result in decreased NEC, shortened time to first and full enteral feedings, and decreased central-line days.

Methods used Our Nutrition QI Team created a rounding tool consisting of a feeding advancement protocol. Infants received DHM if maternal breast milk was unavailable. Central lines were removed when enteral feedings reached 130 ml/kg/day. The QI intervention started September 2016. Outcomes of very low birthweight (VLBW) infants born in the year preceding QI intervention were used as controls.

Summary of results In the first 9 months of intervention, 101 VLBW infants (69 Control group; 42 QI Intervention group) were studied. NEC was reduced by 70% ($p=0.036$; figure 1). Median time to feeding initiation was reduced from 27 hours to 13.5 hours ($p<0.001$). Median time to full enteral feeds and median central line days decreased as well. Weight, length, and head circumference were similar between groups at birth and 36 weeks adjusted age. There were 14 deaths (20.3%) in the control epoch, but zero in the QI intervention group.

Abstract 265 Figure 1 Number of NEC cases per month

Conclusions This QI initiative has significantly reduced NEC and mortality in our NICU to date. Ongoing data collection and analysis continues.

266 EVALUATION OF A STANDARDISED FEEDING ADVANCEMENT GUIDELINE IN PRETERM NEONATES LESS THAN 32 WEEKS GESTATION

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10.1136/jim-2017-000663.266

Purpose of study Feeding advancement is a common conundrum in the NICU. The rate of advancement requires balance between the timely attainment of full feeds and prevention of complications. A standardised approach has been shown to decrease length of stay (LOS) and complications associated with delayed feeding. We aim to determine the effects of a standardised feeding advancement guideline on LOS, time to full enteral feeds, necrotizing enterocolitis (NEC) rates, ventilator days, and central line days in preterm infants less than 32 weeks gestation.

Methods used A mixed retrospective and prospective cohort study including infants born <32 weeks gestation, admitted from 2015 to 2016 from three academically affiliated NICUs. In epoch 1, data was collected retrospectively prior to feeding guideline implementation from January 2015 to December 2015. In epoch 2, data was collected prospectively after feeding guideline implementation from April to December 2016.

Summary of results A total of 253 preterm newborns were included in the study, 160 in epoch 1 and 93 in epoch 2. The implementation of a feeding guideline significantly decreased days to full enteral and oral feeds, number of central line days, and overall LOS without increasing the risk of NEC.

Conclusions This suggests that a standardised guideline can help reduce hospital costs by decreasing LOS without adversely affecting healthcare outcomes.

Abstract 266 Table 1 Demographics in pre (epoch 1) and post (epoch 2) feeding guideline implementation among preterm infants born at

	Epoch 1 n=160	Epoch 2 n=93	P-value
Birth weight (grams)	1005 (725–1312.5)	1017.5 (690–1290)	0.7
Gestational age (weeks)	27 (25–30)	27.6 (25–30)	0.8
NEC (%)	6.52	3.17	0.5
Time to full enteral feeds (days)	46 (24–73)	18.5 (12–21)	<0.0001
Time to full oral feeds (days)	76.5 (50.5–104)	35 (30–47)	<0.0001
Central line (days)	32 (17–51)	12 (6–19)	0.0007
LOS (days)	40 (18–79)	29 (11–58)	0.0197

267 THE IMPACT OF NICU ADMISSION ON BREASTFEEDING INITIATION AND CONTINUATION IN LATE PRETERMS IN 36 U.S. STATES, 2000–2013

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10.1136/jim-2017-000663.267

Purpose of study To compare the rates of breastfeeding (BF) initiation and continuation among mothers of late preterm infants (LPIs) who were cared for in a NICU versus those who were not cared for in a NICU (non-NICU).

Methods used Data from the Pregnancy Risk Assessment Monitoring System (PRAMS) was analysed, including data from 36 states from 2000–2013. Chi-square tests and 95% confidence intervals were used to assess differences in infant and maternal characteristics and BF practices between the NICU and non-NICU LPI groups. Multivariate regression models were used to estimate the independent effect of NICU admission on BF initiation and continuation, controlling for maternal and infant characteristics. All analyses were weighted and standard errors were adjusted to account for the complex survey design of PRAMS.

Summary of results In this sample of weighted n=62 494 LPIs over a 14 year period, 48.6% were cared for in a NICU. For BF initiation, 76.2% of NICU mothers reported initiating BF compared to 71.1% of non-NICU mothers (p-value<0.0001). For BF continuation, 52.0% of NICU mothers reported continuing BF at 10 weeks compared to 55.6% of non-NICU mothers (p-value 0.0001). After adjusting for maternal and infant characteristics, mothers of NICU LPIs were more likely to initiate BF (APR 1.07; 95% CI: 1.05 to 1.09) while there was no difference in BF continuation between the two groups (APR 0.98; 95% CI: 0.94 to 1.0).

Conclusions Mothers of NICU LPIs were more likely to initiate breastfeeding than mothers of non-NICU LPIs but equally likely to continue breastfeeding at 10 weeks. Previous studies have shown that among term infants, 64% of mothers continue BF for at least 10 weeks, a higher percentage than what we have found among both NICU and non-NICU LPIs. It has been well established that LPIs have increased morbidity and mortality as compared to term infants and further work is needed to increase the rates of breastfeeding, and particularly breastfeeding continuation, in this vulnerable population. In addition, future studies are required to better understand why BF initiation is higher in NICU mothers so that newborn nurseries can potentially adopt effective practices that promote BF initiation in this high-risk group.

268 PREDICTORS OF HOME OXYGEN USE AMONG PRETERM INFANTS WITH BRONCHOPULMONARY DYSPLASIA

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10.1136/jim-2017-000663.268

Purpose of study Bronchopulmonary dysplasia (BPD) remains a significant morbidity in preterm infants. Some infants who do not outgrow the condition in the NICU are discharged home

on oxygen. The objective of this study was to identify predictors of home oxygen use among preterm infants with BPD.

Methods used This is a population-based, retrospective cohort study using the California Perinatal Quality Care Collaborative (CPQCC) database from January 2008–December 2016. Infants with BPD born between 22 and 31 weeks in gestation, and who were discharged home were included. Infants with major anomalies or discharged from a non-CPQCC, presently closed, or unknown hospital were excluded. BPD was defined as receiving supplemental oxygen at 36 weeks' postmenstrual age. Primary outcome was discharged home with or without oxygen. Maternal, neonatal, and hospital characteristics were analysed through a multivariable logistic regression model in SAS.

Summary of results The study cohort included 7850 infants. Among which, 3474 (44%) were discharged home with oxygen and 4363 (56%) were discharged home without oxygen. Maternal hypertension (MH), gestational age (GA), sex, birth location (inborn vs outborn), 5 min Apgar score, nosocomial infection, enteral feeding, hospital level of care, ownership, and number of hospital NICU beds were significant risk factors associated with differences in home oxygen use. MH increased odds of home oxygen use by 15% (95% CI: 1.04 to 1.28). Odds also increased with younger GA, as infants born 22–<24 weeks' GA had 3.9 times higher odds of home oxygen discharge than infants born 30–<32 weeks' GA (95% CI: 3.1 to 4.8). Nosocomial infection increased odds of home oxygen use by 26% (95% CI: 1.1 to 1.4), and male infants had 19% higher odds than females (95% CI: 1.1 to 1.3). Compared to government-owned hospitals, investor-owned hospitals had 1.4 times higher odds (95% CI: 1.2 to 1.8) and non-profit hospitals had 1.5 times higher odds (95% CI: 1.3 to 1.8) of home oxygen use.

Conclusions Recognising predictors for home oxygen use in BPD can allow for improved guidance, anticipatory counselling and discharge planning. BPD imposes significant healthcare burden not only during NICU hospitalisation, but in a significant portion of higher BPD severity patients after home discharge.

Neonatology – perinatal biology I

Concurrent session

Friday, January 26, 2018

8:00 AM – 10:00 AM

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EFFECT OF PERINATAL NICOTINE EXPOSURE ON OFFSPRING CARDIAC EXTRACELLULAR MATRIX DEPOSITION

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10.1136/jim-2017-000663.269

Purpose of study Perinatal nicotine exposure affects many organs systems including the developing lung and heart. Although the effects of perinatal nicotine exposure on the developing lung are well studied, there is very limited information on these effects on the developing heart. Increased predisposition to cardiac fibrosis in perinatally nicotine

exposed heart has been shown, but the underlying mechanisms are not completely understood. MiRNAs have an important role in cardiac development and injury repair. Specifically, the miR-29 family is known to target mRNAs encoding extracellular matrix proteins, particularly those involved in fibrosis. We aim to study the patterns of miR-29 expression, along with expression of extracellular matrix proteins involved in cardiac injury and fibrosis, in the hearts of rat pups perinatally exposed to nicotine.

Methods used Pregnant Sprague-Dawley rat dams received either nicotine (1 mg/kg once daily sc) or diluent from embryonic day 6 until postnatal day (PND) 21. Pups delivered spontaneously and were breastfed ad lib. Cardiac tissue was studied on PND 21 by qRT-PCR for specific miR-29 family and Western blot analysis for extracellular matrix proteins.

Summary of results Hearts of rat pups perinatally exposed to nicotine demonstrated decreased levels of miR-29 family (miR-29a, miR-29b and miR-29c, $p < 0.05$ vs controls for all; $n = 8$). Accompanying this, protein levels of collagen types 1 and 3, and fibronectin also increased significantly ($p < 0.05$ vs controls; $n = 4$).

Conclusions Perinatal nicotine exposure is associated with decreased levels of cardiac miR-29 family expression in rat pups. It is also associated with increased cardiac deposition of extracellular matrix proteins such as collagen types 1 and 3, and fibronectin. These findings provide a mechanistic basis for the increased risk of cardiac injury in perinatally nicotine exposed offspring.

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NITRIC OXIDE METABOLISM IN BRAIN, LIVER AND INTESTINE OF ADULT AND FETAL SHEEP

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10.1136/jim-2017-000663.270

Purpose of study Nitric oxide (NO) is an endogenously-produced free radical that is utilised in multiple biological processes. NO exerts its biological function through its primary form (NO•) or as any of several NO metabolites (NO_x). *In vivo*, NO can be metabolised into nitrite, nitrate, nitrosothiols (SNO) and iron-nitrosyls such as dinitrosyl iron complexes (DNIC). Recent studies suggest that DNICs are a major intracellular storage form of bioactive NO. Using novel selective methods of measuring NO_x, the study was designed to characterise the products of intracellular NO metabolism in brain, liver and intestine of the fetus and adult.

Methods used Immediately following euthanasia, liver, ileum, and cerebral cortex samples were collected from fetal and adult sheep. Tissues were homogenised and diluted to 2 µg protein/µL. To evaluate NO• metabolism, 10 µM of the NO• donor Proli-NONOate was added to 1 mL aliquots of each tissue type. NO_x concentrations were assayed at baseline, 1, 5, 10, 20 and 30 min time points. Detection of NO_x was performed using ozone-based chemiluminescence NO• detection by injecting samples into a purge vessel containing reagents that selectively release NO• from nitrite, SNOs or DNICs.

Summary of results NO metabolism was similar between brain, liver, and intestine tissue. A major portion of NO was metabolised to nitrite, SNO and DNIC within 5 min, with the remainder being oxidised to nitrate. The formed DNIC was

also metabolised into nitrite or SNO within 10 min. However, adult brain tissue demonstrated measurable DNICs at 30 min. SNO had greater measured concentration at 30 min in comparison to DNIC and nitrite.

Conclusions In brain, liver and intestine, NO• is rapidly metabolised to nitrite, SNO and DNIC, NO_x that are known to preserve the bioactivity of NO. With the exception of the adult brain, DNIC formed from NO• is rapidly converted to nitrite and SNO. Further studies are needed to characterise specific proteins involved in DNIC and SNO formation, and the extent to which they contribute to NO signalling.

Abstract 270 Figure 1 Nitric oxide metabolism to nitrate, nitrite, nitrosothiols, and dinitrosyl iron complexes

271 THE IMPACT OF CHRONIC IGF1 INFUSION ON FETAL SHEEP PANCREATIC BETA-CELL MASS

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10.1136/jim-2017-000663.271

Purpose of study Fetal insulin secretion is critical for the regulation of somatic growth. Insulin secretion is partly determined by the amount of β-cells present, or β-cell mass. Insulin-like growth factor-1 (IGF1) is an important endocrine and paracrine fetal growth factor which regulates β-cell mass. However, the extent to which elevated circulating concentrations of IGF1 impacts fetal β-cell mass is unknown. We hypothesised that chronic infusion of IGF1 for one week into fetal sheep circulation would increase β-cell mass.

Methods used Chronically catheterized late gestation fetal sheep were infused with either 6.6 ug/kg/hr of IGF1 Long R3 derivative (LR3, n=8) or saline as a control (CON, n=10) for one week. IGF1 LR3 was used to minimise binding to IGF binding proteins while maintaining high IGF1 receptor affinity. On the last day of infusions (133 days gestation; term=148 days), fetal arterial plasma glucose and insulin were measured. The fetal pancreas was fixed in paraformaldehyde and cryopreserved. Four sections were used for immunostaining with an anti-insulin antibody and a fluorescent secondary antibody to determine the percent area of pancreas staining positive for insulin (β-cell area) using CellSense software to evaluate the entire section. β-cell mass was calculated as the product of this and pancreatic mass. Means were compared with Student's T Test.

Summary of results Plasma insulin (0.07±0.01 ng/ml IGF1 vs 0.45±0.11 ng/ml CON, p<0.005) and glucose (0.7±0.1 mmol/L IGF1 vs 0.9±0.1 mmol/L CON, p<0.05) concentrations were lower in IGF1-infused fetuses, but body weights, pancreatic weights, and pancreas-to-body weight ratio were not different between groups. There were no differences in β-cell area (5.3%±0.57% IGF1 vs 4.66%±0.65% CON) or mass (186±21 mg IGF1 vs 178±31 mg CON).

Conclusions Fetal infusion of IGF1 LR3 for one week in late gestation lowers insulin and glucose concentrations but does

not increase β-cell mass. The previously described role for IGF1 as a β-cell growth factor may be more relevant for local paracrine action in the pancreas as opposed to circulating endocrine actions of IGF1. This is in contrast to the growth-promoting effect of circulating IGF1 on other fetal tissues described previously.

272 LEUCINE POTENTIATES GLUCOSE STIMULATED INSULIN SECRETION IN FETAL SHEEP, BUT NOT IN MIN6 CELLS

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10.1136/jim-2017-000663.272

Purpose of study Amino acids potentiate fetal glucose stimulated insulin secretion (GSIS). However, the ability of individual amino acids to potentiate fetal GSIS has not been tested. The objective of this study was to determine if supplemental leucine (LEU) would potentiate GSIS in late gestation fetal sheep *in vivo* and in the insulin secreting cell line, MIN6.

Methods used Late gestation fetal sheep (n=5) were catheterized and square wave hyperglycemic clamps were used to measure GSIS during infusions of LEU (752 μmol/h) or saline (SAL, 0.3 mL/h) started 90 min prior to the clamp on different days in the same animal. At 60%–70% confluence MIN6 cells were placed in DMEM±supplemental leucine (10 mM) or a combination of the three branched chain amino acids (BCAAs – Leucine, Isoleucine, Valine, 30 mM) for 24 hours. Insulin secretion was then measured in Krebs Ringer Bicarbonate Buffer without nutrients except low or high glucose (2.8 or 16.7 mM) or KCl (30 mM), as a positive control for maximal insulin stimulation, for one hour. Insulin secretion is expressed as a percentage of the insulin released into the media out of total insulin present in the cells.

Summary of results During the hyperglycemic clamp, plasma concentrations of glucose were similar between LEU and SAL infusions, but plasma concentrations of insulin were 33% higher during the LEU infusion compared to SAL (p<0.001). MIN6 cells incubated without leucine or BCAA supplementation secreted more insulin with high glucose or KCl compared to low glucose (p<0.05). However, MIN6 cells incubated with supplemental BCAAs did not secrete more insulin in response to high glucose compared to low glucose and MIN6 cells incubated with leucine actually secreted less insulin with leucine in response to high glucose compared to low glucose (p<0.01).

Conclusions These results indicate that leucine potentiates fetal GSIS *in vivo* and show how multiple nutrients like glucose and leucine can act in concert to increase fetal insulin concentrations. However, MIN6 cells had a paradoxical inhibition of GSIS after incubation in supplemental leucine, indicating that other *in vivo* factors during the leucine infusion might be acting to stimulate GSIS that are not replicated *in vitro*.

273 THE HOXA3 HOMEBOX AFFECTS LUNG DEVELOPMENT VIA THE NOTCH PATHWAY

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10.1136/jim-2017-000663.273

Purpose of study To determine the expression of key Notch signalling intermediates and characterise alveolar epithelial-mesenchymal differentiation in HoxA3 KO mice.

Methods used Mice, heterozygous for HoxA3 knockout were bred, delivered via caesarean section at embryonic day 18.5, and embryos genotyped. The lungs of the embryos were harvested and evaluated for key Notch pathway intermediates (qRT-PCR for Jag1, Jag2, Fgf8, Fgf10, Dll1, Dll3, Dll4, Hey 1, Hey 2, Hes1, Hes2, HeyL, Notch1, Notch2, Notch3, Notch4, Dtx1) and markers of epithelial (surfactant protein A, B, and C) and mesenchymal (PPAR γ , ADPR, CBP- α) differentiation by qRT-PCR. Rate of surfactant phospholipid synthesis by the harvested lung explants was determined by measuring [3 H]choline incorporation into saturated phosphatidylcholine and [3 H]triolein uptake.

Summary of results Our data suggest upregulation of Fgf8, Dll1, Dtx1, and Hey1 ($p < 0.05$ in HoxA3 knockouts versus controls). Surfactant protein B and CBP- α were upregulated in mutants ($p < 0.05$ vs control mice). This was accompanied by the down-regulation of triolein uptake with a trend towards significance ($p = 0.07$ vs control mice).

Conclusions Our data suggest that the HoxA3 homeobox gene affects lung development via the Notch pathway. To determine the spatio-temporal localization of molecular alterations, further studies are in progress using immunofluorescence staining and *in-situ* hybridization for lung development markers as well as the Notch pathway intermediates.

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THE EFFECTS OF HYPOXIA, PREGNANCY, POTASSIUM, AND RYANADINE ON CALCIUM SPARK RELEASE FROM UTERINE ARTERIAL MYOCYTES

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10.1136/jim-2017-000663.273A

Purpose of study Previous work from our group has shown that pregnancy enhances vasorelaxation of uterine arteries, while chronic high-altitude exposure depresses vasorelaxation. These changes in vasodilatory capacity are caused by modifications to the activity and expression of the large conductance Ca $_2$ +activated potassium channel (BK).

There have been some data discrepancies between the activity and the expression of the BK channels. Thus, we wanted to investigate whether the mechanisms that activate the BK channels were also affected by pregnancy and hypoxia. Activation of ryanodine receptors (RyR) on the sarcoplasmic reticulum causes local Ca $_2$ +release events, called Ca $_2$ +sparks, that are tightly coupled to BK channel activity and concomitantly to membrane hyperpolarization. This process ultimately results in vasorelaxation. The aim of this work was therefore to test the hypotheses that in uterine arterial myocytes:

1. Membrane depolarization increases calcium spark activity
2. Ryanodine, a putative ryanodine receptor inhibitor, inhibits calcium sparks
3. Pregnancy increases calcium spark activity
4. Hypoxia suppresses calcium spark activity.

Methods used Uterine arteries were isolated from pregnant and non-pregnant sheep that were kept under either normoxia or exposed to 3,801 m for 100+days. Following isolation,

arteries were denuded of endothelium and the remaining myocytes were loaded with a calcium sensitive dye (fluo4 AM). Then, they were treated with one of 3 solutions: Saline solution (Ctrl), depolarizing 30 mM potassium (30 K), or 30 mM potassium with 10 mM ryanodine. Using confocal microscopy, line scans were recorded and images were analysed for Ca $_2$ +sparks using SparkLab.

Summary of results Our results showed a significant increase in the frequency of sparks with pregnancy. Spark frequency was increased in all groups by 30 mM potassium and reduced by ryanodine. Hypoxia had a varied effect on frequency between the groups.

Conclusions This work supports the premise that ryanodine receptor and BK channel activities change in parallel in response to pregnancy or hypoxia..

Surgery III – general surgery, transplant, urology

Concurrent session

Friday, January 26, 2018

8:00 AM – 10:00 AM

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IS THERE A ROLE FOR THE ROBOT IN ACUTE CARE SURGERY?

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Purpose of study To determine if the use of the surgical robot can add value to the Acute Care Surgery service at a busy academic hospital by studying OR time, length of stay, complications, and hospital costs.

Methods used We reviewed a prospectively collected Acute Care Surgery registry at a large (>500 bed) adult university hospital over 9 months. Cases from two acute care surgeons were included. Operative technique could not be randomised as trained robotic personnel are available only on weekdays. We collected data on demographics, indication for surgery, nutritional status, comorbidities, OR time, postoperative complications, length of stay, and costs (day of surgery until discharge). We analysed our data in SPSS 22 (IBM Inc., Armonk NY) and utilised Student's T test and Chi-Square. We performed a linear regression analysis to determine the effect of OR time, robotic surgery, and diagnosis on operating room costs and postoperative length of stay.

Summary of results 37 laparoscopic and 14 robotic cholecystectomies were performed. Demographic parameters were comparable. Primary diagnosis was significantly different (Chi-square 0.05), driven by more acute cholecystitis in the laparoscopic group. 0/14 robotic cases and 5/37 (13.5%, $p = 0.305$) laparoscopic cases were converted to open procedures. There was no difference in the incidence of postoperative complications. Operative time was similar (158 ± 38 min [robot] vs. 135 ± 62 min [lap], $p = 0.125$). There was a trend toward shorter postoperative length of stay in the robotic group (1.4 ± 1.4 days vs 2.4 ± 2.6 days, $p = 0.087$) but this was not significant

even after adjusting for OR time and diagnosis. Robotic procedures had higher unadjusted OR costs (\$3490±\$934 vs \$2190±\$831, $p<0.001$). Adjusting for OR time and diagnosis, robotic surgery was associated with a \$980 increase in costs [95% CI: \$648 to \$1310, $p<0.001$].

Conclusions Robotic cholecystectomy can be safely performed on an ACS service with minimal risk of conversion. Robotic surgery is independently associated with increased OR cost, but individual hospital systems must decide if this additional cost outweighs increased robot utilisation and training benefits for physicians and staff.

275 IMMUNE AND ENDOCRINE MARKERS AS A PREDICTOR OF FRAILTY IN GERIATRIC TRAUMA PATIENTS

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Purpose of study Frailty is a geriatric syndrome described as a state of decreased physiological reserve is associated with morbidity and mortality. Frailty has been associated with inflammatory and endocrine markers, which can be utilised as predictors of frailty. The aim of our study was to analyse the association of frailty with immune biomarkers (IL-1 β , IL-6, IL-2R α , TNF- α) and endocrine markers (IGF-1, GH).

Methods used We performed a one-year prospective analysis of all geriatric trauma patients admitted to our level-1 trauma centre. We excluded patients who had GCS<15 or were transferred from other facilities. Frail status was calculated using validated Trauma Specific Frailty Index (TSFI). Frailty was defined as Frailty Index>0.27 Serum samples were collected within 24 hours of injury. We measured the levels of biomarkers by a colorimetric output that was read by a spectrophotometer.

Summary of results We analysed a total of 20 geriatric trauma patients. Median age was 72 [65–85], 55% were females. Median FI was 0.24 [0.03–0.75]. Overall 55% (9/20) patients were stratified as frail. There was no difference between the age ($p=0.78$), gender ($p=0.77$), race ($p=0.98$), mechanism of injury ($p=0.81$), ISS ($p=0.71$), systolic blood pressure ($p=0.85$), and heart rate ($p=0.91$) between the two groups. Frail patients had a higher IGF-1 level compared to non-frail patients (72 ± 7.3 vs 53 ± 6.1 , $p=0.01$). However, there was a trend towards higher TNF- α , IL-6, and IL-1 β , and trends towards lower IL-2R α , and GH in frail patients.

Conclusions This pilot study supports the association between immune and endocrine markers and frailty. These findings have significance for early identification of frailty using circulating biomarkers prior to clinical manifestations of severe physiological decline in the geriatric trauma patients.

Abstract 275 Table 1 Immune and endocrine markers in frail and non-frail patients

Markers (mean±SEM)	Non-frail	Frail	p-value
TNF- α , pg/ml	22.7±3.4	29.9±4.7	0.11
IL-6, pg/ml	9.8±4.3	14.5±5.6	0.52
IL-2R α , pg/ml	11.1±3.9	10.8±4.1	0.95
IL-1 β , pg/ml	7.5±0.95	9.7±1.2	0.16
GH, pg/ml	57±11.8	49±7.3	0.59
IGF-1, ng/ml	72±7.3	53±6.1	0.01

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EFFECTS OF INTRAOPERATIVE BLOOD PRODUCT ADMINISTRATION ON OUTCOMES IN PATIENTS UNDERGOING ORTHOTOPIC LIVER TRANSPLANTATION

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10.1136/jim-2017-000663.276

Purpose of study Orthotopic liver transplant (OLT) is the only effective long-term treatment option for chronic and acute end-stage liver disease. OLT is associated with massive blood loss and large transfusion volumes. Large blood transfusions have inherent risk and have been associated with increased morbidity and mortality. Previous studies examining the sometimes deleterious effects of large blood transfusions in OLT have led to a decrease in intraoperative blood product administration. This study investigates whether reductions in blood product administration lead to decreased intensive care length of stay (ICU LOS), hospital length of stay (HLOS), and improved discharge disposition. In addition, this study examines a potential method of determining which patients have an increased risk of requiring large blood transfusions.

Methods used To gauge the effectiveness of reducing blood transfusions, we reviewed perioperative liver transplant data for 124 patients that underwent OLT between January 2012 and December 2016. Patients were separated into two groups, a massive transfusion cohort (greater than ten units of packed red blood cells transfused during transplant) and a non-massive cohort (less than ten units of packed red blood cells transfused during transplant). Patient's Model for End-Stage Liver Disease (MELD) scores, surgical technique utilised, ICU LOS, HLOS and discharge disposition for each cohort were then compared.

Summary of results After analysis, the Model for End-Stage Liver Disease (MELD) score was significantly higher in the massive transfusion group versus the non-massive transfusion group ($p=0.013$). We also noted a significant increase in HLOS in the massive transfusion group ($p=0.031$). The surgical technique utilised (Piggyback vs Veno-venous Bypass), ICU LOS and discharge disposition or mortality was not found to be significantly different.

Conclusions Increased hospital LOS is likely due to increased post-operative complications and likely led to increase overall cost for care. This study appears to corroborate other studies, which note that massive transfusion negatively effects patient outcome. Additionally the results suggest that patients with higher MELD scores are at increased risk of requiring massive transfusions.

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COMPARATIVE EFFECTIVENESS OF CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA AND LOCALLY ADVANCED PRIMARY TUMOURS

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Purpose of study The survival benefit of cytoreductive nephrectomy (CN) for the subgroup of metastatic renal cell cancer (mRCC) patients with locally advanced primary tumours (stage classification T3/T4) has not been clearly elucidated. This leads to substantial provider uncertainty considering the

Abstract 277 Figure 1 Treatment group I systemic therapy first ± cytoreductive nephrectomy first

surgical management of mRCC patients with locally advanced primary tumours. This retrospective cohort study sought to compare overall survival (OS) among advanced mRCC patients treated with upfront CN versus upfront systemic therapy.

Methods used Using linked SEER-Medicare data, we identified mRCC patients with stage classification T3/T4 tumours diagnosed between the years 2004–2011. We compared OS between treatment groups by constructing unadjusted Kaplan-Meier curves and multivariate Cox proportional hazards regression models adjusting for patient demographic and clinical parameters. Comparisons with therapy groups were further limited to patients with part D data.

Summary of results 1545 cases met our initial inclusion criteria, including 976 CN patients. The median OS for CN patients was 12 months versus 6 months for non-CN patients with an adjusted hazard ratio of 0.67 (95% CI: 0.59 to 0.76). We examined a more refined subgroup restricted to CN patients with observed post-CN systemic therapy versus upfront systemic therapy, and we identified a survival benefit to CN (hazard ratio 0.69, 95% CI: 0.49 to 0.95).

Conclusions Despite the poor prognosis of mRCC with advanced primary tumours, CN appears to confer better OS compared with initial systemic therapy.

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BENCH-TOP STUDY USING THE NOVEL LASER DARRT TO REDUCE RADIATION EXPOSURE DURING PERCUTANEOUS RENAL ACCESS

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Purpose of study Radiation exposure from the diagnosis, treatment, and follow-up of kidney stones can result in the development of radiation-induced malignancy in patients. It is therefore important to reduce radiation during kidney stone treatment. We have developed a novel technique to obtain renal access that we call the laser direct alignment radiation reduction technique (DARRT), which aims to reduce radiation exposure when

obtaining renal access during percutaneous nephrolithotomy (PCNL). The purpose of this study was to compare the laser DARRT to a modified laser-less ring DARRT and continuous conventional fluoroscopy during PCNL.

Methods used The laser DARRT was compared to conventional fluoroscopy and laser-less ring DARRT in accessing the upper, middle, and lower poles of a kidney. Six attending physicians, 6 residents, and 10 medical students obtained access using a phantom renal model with simulated rib interference. Laser DARRT uses a patented needle with a C-arm laser beam and pulsed fluoroscopy to gain renal access. The primary endpoint was total fluoroscopic time while secondary endpoints were total needle insertion time, number of punctures, number of course corrections, and subjective ease-of-use.

Summary of results The laser DARRT reduced total fluoroscopic time by 89.8% compared to conventional access. Fluoroscopic time was significantly lower for all three groups: attendings (23.56 vs 3.33 vs 2.39 s; $p < 0.001$), residents (17.17 vs 3.39 vs 2.11 s; $p < 0.001$), and students (23.97 vs 3.63 vs 2.22 s; $p < 0.001$) with respect to conventional, ring DARRT, and laser DARRT access. Total needle insertion time varied by group: attendings (28.28 vs 28.61 vs 25.17 s; $p = 0.823$), residents (28.72 vs 31.67 vs 39.44 s; $p = 0.228$), and students (25.67 vs 33.17 vs 36.83 s; $p = 0.014$). There was no significant difference between groups in the number of course corrections or number of punctures needed to reach the calyx. All groups preferred the laser DARRT over other techniques.

Conclusions The laser DARRT reduced total mean radiation time by 89.8% without compromising accuracy. This technique can simplify renal access and reduce the risk of radiation exposure from PCNL.

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CHRONIC INDWELLING URETERAL STENTS: DOES STENT TYPE MATTER FOR ENCRUSTATION?

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Purpose of study Ureteral stents are placed to maintain ureteral drainage and relieve obstruction. Chronic indwelling stents may result in complications including fragmentation, migration, and encrustation. Other than indwelling time, factors contributing to stent encrustation are unknown. The purpose of this study is to compare the risk for encrustation and force required for removal in soft, firm, multi-length, and fixed length stents.

Methods used Sixteen double pigtail stent coils were used in an *in vitro* urine bath to determine risk for encrustation. Four firm multi-length, firm fixed-length, soft multi-length, and soft fixed-length stent coils were used for a total of 16 coils. A urine bath was established with urine from 5 healthy volunteers and urease. All sixteen stent coils were placed in the urine bath and stored in an incubator at human body temperature for 15 days. The force required for stent extraction from a ureteral benchtop model was measured by a force gauge before and after the urine bath.

Summary of results After 15 days, all stents had <5 mm encrustation. The mean force required for stent removal after the urine bath was 0.658 n, 0.688 n, 0.306 n, and 0.200 n respectively for firm multi-length, firm fixed length, soft multi-length, and soft fixed length coils. Firm stents required less force for removal than soft stents prior to the urine bath (0.216 n firm versus 0.245 n soft; $p < 0.001$), but more force after the urine bath (0.669 n firm versus 0.266 n soft; $p < 0.001$) regardless of whether these stents were fixed or multi-length. Soft stents, however, increased in length from a mean of 9.0 cm to 12.4 cm ($p = 0.003$) whereas firm stents were consistent in length (9.0 cm to 9.0 cm; $p = 0.709$). Soft stents also increased in diameter from 2.0 cm to 3.0 cm ($p = 0.004$).

Conclusions Stent encrustation occurred as early as 15 days. While firm stents required more force for removal, soft stents demonstrated significant spatial changes *in vitro*.

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MECHANISMS OF CHEMOTHERAPY-INDUCED BLADDER DYSFUNCTION IN CHILDREN

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10.1136/jim-2017-000663.280

Purpose of study Paediatric bladder dysfunction is a serious problem which affects long-term patient health as well as patient and caregiver productivity and health-related quality of life. Childhood cancer survivors treated with chemotherapy exhibit unexpected signs and symptoms of bladder dysfunction. In connecting the exposure of cytotoxic chemotherapy to potential bladder dysfunction, there are two widely used agents in paediatric oncology, Vincristine (VCR) and Doxorubicin (DOX). The goal of this project is to determine the mechanisms of action of chemotherapeutic drugs on bladder function using animal models in order to establish a background for future work aimed at prevention of chemotherapy-induced bladder dysfunction in children.

Methods used Utilising a murine model of exposure to VCR and DOX, both individually and in combination, we studied bladder function directly *in vivo* and *ex vivo* utilising established assays evaluating myotonic and neurogenic bladder function. A comprehensive evaluation of urinary bladder function using non-invasive (filter paper assay, metabolic cages) methods was supplemented by *in vitro* studies on isolated detrusor muscle strips over an 8 week period. We will compare

functional changes in the urinary bladder between experimental and control mice.

Summary of results 72 mice were recruited (39 male, 33 female). In 12 surviving mice, filter paper analysis over a 3 hour span indicated that urinary volume in control group was 57% of that in experimental group at time intervals throughout the study (3 w, 5 w, 6 w, 8 w). Detrusor muscle strip contractility force in the experimental group was 81% of that in the control group. Electrical stimulation of detrusor muscle strips when coupled with nicotinic blocks (TMPH) resulted in a 12% decrease in muscle contractility.

Conclusions Doxorubicin may have small underlying effects on the murine detrusor, as demonstrated by lower contraction forces when exposed to stimulation in high concentrations. Doxorubicin may have effects on urinary retention, leading to increased voiding volumes. The effects of Vincristine on the murine detrusor are currently being investigated. Additionally, the urinary protein profile will be investigated between the control and experimental groups.

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A DURABLE, LOW-COST TRAINING MODEL FOR PERCUTANEOUS RENAL ACCESS

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10.1136/jim-2017-000663.281

Purpose of study Obtaining access into the renal collecting system is technically challenging. Currently, interventional radiologists and urologic surgeons acquire most of their operative training during surgical cases on live patients. This training paradigm may compromise patient safety. The purpose of this study was to design and implement a low-cost training phantom model for gaining percutaneous renal access that could improve a trainee's technical skills without compromising patient safety.

Methods used A model renal collecting system was fashioned from a surgical glove filled with contrast-enhanced (30%) ballistic gelatin. The gelatin was formulated 1 part ballistic gelatin powder to 9 parts hot water by weight. The collecting system was then placed into a large container which was filled with ballistic gelatin that did not contain contrast. After the gelatin set, the finished block was placed into a model with a clear acrylic glass base, open side, and a cover of polyethylene foam. Two-centimeter-wide chalk pieces were incorporated into the cover to simulate ribs. Participants were taught to access each renal calyx with a needle under fluoroscopic guidance. Successful renal access was confirmed by direct visualisation through the side or the acrylic glass base. The primary outcomes were feasibility, cost, durability, and subjective similarity to clinical renal access.

Summary of results Ballistic gelatin proved to be a durable and accurate medium for PCNL training. Each gelatin block sustained over 200 needle punctures with no observable compromise in structure. The contrast-enhanced gelatin collecting system did not leak when pierced by a needle allowing back to back trials without loss of integrity. In addition, the simulated ribs were clearly visualised on fluoroscopy and added an additional layer of complexity to renal access. The supplies required to construct four models cost approximately 300 dollars. The model was considered robust, realistic, and an effective training model for renal access.

Conclusions This low-cost model was durable and effective. Use of this model could avoid skills acquisition in live patients and subsequently improve patient safety during percutaneous renal access.

Behaviour and development I

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

282 DEVELOPMENT AND BEHAVIOUR DIAGNOSES USED BY PAEDIATRIC PRIMARY CARE PROVIDERS: EXPLORING INTER-CLINICIAN VARIATION

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Purpose of study Limited objective data exist on variation across paediatric primary care clinicians when diagnosing developmental and behavioural (DB) conditions.

Aims

- determine numbers of DB diagnosis codes used by clinicians (n=75) in a network of paediatrics offices (n=21)
- describe inter-clinician variation in coding
- examine clinician characteristics and assess their independent contributions to DB diagnosis coding rates.

Methods used Retrospective analysis of electronic medical records of all encounters documented by network clinicians in one year (10/1/15–9/30/16).

Dependent variables Proportion of unique children, per clinician, with visit diagnoses of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), or developmental delay/concern (DD).

Independent variables clinician gender, years in practice, and full time equivalent (%FTE).

Analysis (Aims 1, 2) frequencies, proportions. (Aim 3) Multivariate linear regression models to predict variation in use of DB diagnoses.

Summary of results

- Among 44,856 children age 4–18 years, 456 (1.0%) had ASD diagnosis; 1597 (3.3%) had ADHD diagnosis. Among 18,130 children under 4 years, 1065 (5.6%) had DD diagnosis.
- Across clinicians, code use was highly variable; ASD, ADHD, and DD diagnosis proportions ranged from 0%–4.4%, 0%–11.8%, and 0%–17.2%.

- Regression models including clinician gender, %FTE, and years in practice explained 11%, 23%, and 6% of variation in use of ASD, ADHD, and DD codes (table 1).

Conclusions Primary care Identification of common DB conditions is lower than estimated prevalence rates and is highly variable; clinician characteristics contribute to this variation. Further study of other clinician, clinic, and patient characteristics is needed to identify modifiable factors that present barriers to providing DB-related care.

283 EVALUATING THE IMPACT OF PHYSICIAN WELLNESS WORKSHOP ON PSYCHIATRY RESIDENTS WITHIN A TERTIARY CARE CENTRE

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10.1136/jim-2017-000663.283

Purpose of study There has been an alarming increase in the rates of depression and symptoms of burn-out among physician trainees. Despite efforts to address this, studies show that there remain gaps in fully understanding effective interventions in this population. It is well known that physicians, who are best able to take care of their personal health, are better equipped to take care of their patients. Furthermore, physicians who experience physical and mental health are less likely to experience burnout and make less medical errors.

Methods used This study sought to evaluate the effectiveness of a 9-session, Wellness Workshop on the personal habits and experiences of first to fourth year Psychiatry resident physicians. Sessions were held during lunch and included training on exercise, healthful eating, positive relations, coping techniques, amongst other personal wellness interventions. Participants were then invited to complete an anonymous online survey and results were grouped for analysis.

Summary of results A total of 9 residents responded to our survey. 50% of respondents were interns and junior residents (PGY-1, PGY-2) and 50% were senior residents (PGY-3, PGY-4). 77% of residents strongly agreed that the workshop was a positive experience and 88% reported that they would use the skills and information learned in their future careers. 67% reported feeling burnout at the start of the workshop, and 55% considered themselves to be burnt out currently. 77% of residents reported an improvement in their ability to promote their own personal wellness and better manage their stress. 78% of residents stated that they are better able to help their patients deal with stress as a result of the program and 89% shared that they would participate in a workshop of this nature in the future.

Abstract 282 Table 1 Multivariate linear models of clinician factors predicting use of DB diagnosis codes*

Variables	ASD		ADHD		DD	
	β	P	β	P	β	P
Clinician gender**	−0.078	0.527	−0.235	0.043	0.155	0.223
Clinician FTE percent	0.190	0.111	0.333	0.003	0.174	0.154
Clinician years in practice	0.243	0.049	0.153	0.181	−0.077	0.538

*Use of DB Diagnosis Codes=Number of unique patients with diagnosis/Number of all unique patients seen in 12 months. **Reference group is male clinicians (male 0, female 1).

Conclusions Our study suggests that Resident Wellness Workshops are a beneficial intervention and assists with the development of practical skills to promote resilience among medical trainees. More study is needed to further elucidate specific strategies that are beneficial as well as explore barriers to seeking support among physicians in training.

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EVALUATING THE IMPACT OF PLANT-BASED NUTRITION AND CULINARY EXPERIENCE IN MEDICAL SCHOOL EDUCATION

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10.1136/jim-2017-000663.284

Purpose of study To determine the impact of plant-based nutrition and culinary experience on medical student ability to engage and counsel patients on lifestyle-related diseases and its impact on health.

Methods used We conducted a retrospective cohort study to evaluate the efficacy of lecture based nutrition presentation and adjunct participatory culinary experience in the training of senior medical students at Loma Linda University Medical School. A total of 42 students took part in this experience and were given pre- and post- assessments of their knowledge, skills and confidence in counselling patients about the effect of diet on their chronic disease. Personal health behaviours and practices among medical students were also assessed. Results were reported anonymously and grouped for the final analysis.

Summary of results A two sample t test was used to compare pre and post intervention scores. Medical students self-reported improved ability to answer patient questions related to nutrition and dietary choices was 24% greater after the interventions than before ($p < 0.0001$). In addition their confidence in counselling patients on the effects of dietary choices on lifestyle related diseases increased by 10% following this educational experience ($p = 0.0015$). While there were increases in their personal health behaviours and choices, these findings were only marginally significant ($p = 0.0568$).

Conclusions In this small pilot study, a combination of lecture-based nutrition education, and participatory culinary experience improved medical students' knowledge and confidence in answering questions related to the plant-based diet and its effect on lifestyle related chronic diseases. While there appears to be some improvement in the personal health attitudes and behaviours of trainees, additional research and evaluation is needed.

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HOW EFFECTIVE ARE HEALTH PROFESSIONAL STUDENTS IN COPING WITH STRESS?

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10.1136/jim-2017-000663.285

Purpose of study Health care professionals today deal with a health care system that is in transition, with increasingly larger demands including longer hours, heavier workloads, and limited control over their work environment. These conditions have shown a direct link to increased stress and burnout, which has a negative effect on the provider and quality of patient care. Furthermore, stress in the preclinical years

follows students as they progress their health careers. This study examines the most common stressors present among two professions, with analysis comparing the effectiveness of self-care strategies between osteopathic medical and optometry students.

Methods used Our study's framework was adapted from the COPE scale developed by CS Carver. The scale consists of 14 categories of coping strategies on a Likert scale ranking from 0 to 4, with score of 4 meaning complete alleviation of stress. The survey was directed towards WesternU optometry and medical students through a school-wide email. Statistical analysis was done through a t-test. Our null hypothesis states there is no difference in mean Likert scores of coping strategies between osteopathic medicine and optometry students.

Summary of results The response rates for College of Osteopathic Medicine and the College of Optometry were 179 and 107 responses respectively, with high volume of material in a short time period as the most common stressor. The most effective coping mechanism for medical and optometry students was active coping (Likert score of 2.63 and 2.57 respectively).

Conclusions There was no significant difference in the effectiveness of self-care strategies between College of Osteopathic Medicine and College of Optometry with $p = 0.706$. In the future, we hope to study more professions, and further understand any possible differences between professions to apply techniques to empower health students on effective self-care strategies.

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PRETRANSPLANT DEPRESSION, STRESS, AND ANXIETY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

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10.1136/jim-2017-000663.286

Purpose of study Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a demanding treatment for cancer patients with hematopoietic malignancies. Allo-HSCT patients are at high risk of infection, graft vs host disease, and poorer survival. In many cases, Allo-HSCT is one of the final treatment options for these patients. Going into the transplant, these patients experience significant stress, which may have an impact on the treatment and the outcomes. This study is to analyse the baseline psychological characteristics of these patients and their relationships.

Methods used Prior to transplant, psychological measures were collected from Allo-HSCT patients ($n = 159$) using the Perceived Stress Scale (PSS), Centre for Epidemiologic Studies Depression Scale (CESD), and State-Trait Anxiety Inventory (Stai_S). Information on their demographics was also collected at baseline. Chart review information was also available.

Summary of results The mean age of the patients was 53.3 years old ($SD = 14.8$), with 64.8% were male. Diagnoses included 97 had leukaemia, 21 had lymphoma, 35 had myelodysplastic syndrome or myeloproliferative syndrome, and 6 had other diagnoses such as multiple myeloma and severe aplastic anaemia. The mean PSS was 21.7 ($SD = 8.0$), placing them in the range for moderate stress. CESD mean score was 20.4 ($SD = 6.7$), which exceeds the clinical cutoff of 16 or greater. The mean anxiety score was 36.8 ($SD = 11.6$), which also exceeds population norms for this age

group. There is significant correlation between CESD and PSS ($r=0.550$, $p=0.000$) and between CESD and Stai_S ($r=0.529$, $p=0.000$). PSS and Stai_S are also significantly correlated ($r=0.686$, $p=0.000$).

Conclusions Allo-HSCT patients at baseline have elevated Perceived Stress and Stai_S scores as well as high CESD score. These values indicate that the Allo-HSCT patients prior to transplant are experiencing stressors that are affecting their psychological health, which may affect their treatment outcomes. There are significant correlations between depression, perceived stress and anxiety, which help demonstrate that these psychological measures are often comorbid. Further studies are needed to explore how the baseline measures of Allo-HSCT affect treatment outcomes. (Supported in part by a contract from PCORI CE-1304-6208.)

287 THE BURDEN OF CAREGIVING: IS IT TOO MUCH TO BARE? PROVIDING CARE FOR CHRONICALLY AND TERMINALLY ILL FAMILY MEMBERS

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10.1136/jim-2017-000663.287

Purpose of study To determine the level and predictors of burden in providing care to chronic and terminal ill family members.

Methods used We analysed data from 1997, 2004 and 2009 Care Giving in U.S survey (cross sectional design using telephone interview of a random sample of family caregivers ≥ 18 years old). Caregiver was defined as those who provide unpaid care to a relative/friends with illness/disability in the past year. Burden was defined as the number of hours spent/week, delivering assistance with specific tasks and the number of activities and instrumental activities of daily living performed. The main illness/problem of recipient was categorised as: None, chronic, terminal and other. Variables included in the analysis were race, age, employment, education, marital status, health status of caregivers, and illness of the recipient. Data were analysed using SPSS V22.

Summary of results Of 3981 participants, 68% were women, 78% were white, 46% were ≥ 50 years, 35% had $\leq$ high school education, 25% were unemployed, 10% reported fair/poor health status, 44% cared for a family with chronic condition, 9% cared for family with terminal illness, and 50% reported medium/high burden (56% for chronic condition, and 68% for terminal illness, $p<0.05$).

Relative to care for family with no condition, those who care for family with chronic condition or terminal illness had 2 and 4 times higher adjusted odds to report medium/high burden respectively ($p<0.05$). Predictors of reporting medium/high burden were race/ethnicity (Hispanic/Blacks), age (≥ 50 years), education ($\leq$ high school), unemployment, and health status (poor/fair) ($p<0.05$).

Conclusions Medium to high levels of burden was reported by Hispanics and African-Americans caregivers caring for a family with terminal or chronic illness who self-perceived their own

health as fair/poor. Research is needed to address cultural perspectives of caregiving, determine best practices of caregiving for chronic and terminal recipients. Specific guidelines are needed to help resolve problems resulted from caregiver's strain and burden especially when they care for family with terminal or chronic illness.

288 EMPOWERMENT-BASED NUTRITION EDUCATION SERIES IN A PEER SUPPORT GROUP SETTING FOR TYPE 2 DIABETES

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10.1136/jim-2017-000663.288

Purpose of study The Empowerment-based Nutrition Education Series (EBNES) aims to actively teach those with type 2 diabetes in Kemmerer, WY about type 2 diabetes with nutrition, weight management, portion control, and support information as well as promote informed and empowered lifestyle changes for management. Kemmerer, WY is a town of 2600 people in Lincoln County with a county diabetes rate of 8.6% in 2015, which is above state average and highlights a need for education in this area.

Methods used Through community conversations with the Public Health Nurse (PHN) for Lincoln County-Kemmerer, clinic observations, and visiting the Diabetes Support Group run by Lincoln County Public Health, it became clear there was a population in Kemmerer with an unmet desire and need for information to empower their decisions. A literature search was completed to examine successful peer support group education based on diabetes management outcomes such as lower weight, lower HbA1c values, and more confidence in lifestyle choices. Effective methods that had been published involved empowerment based learning styled after motivational interviewing techniques, peer discussions, revisiting topics of relevance annually, and inventory quizzes.

Summary of results PowerPoint presentations were created on nutrition, weight management and exercise, portion control, and support that included information as well as group discussions, short inventory quizzes, possible barriers to lifestyle changes, how to overcome obstacles, additional resources, and a script for the PHN to present. These were presented and then given to the PHN to deliver as a series over the course of 3 meetings. The completed literature review was also delivered to the PHN.

Conclusions The strengths of the EBNES were that it focused on group support and allowed individuals to make the best-informed decisions for themselves, giving them empowerment and the knowledge to help manage their diabetes with lifestyle changes. Challenges to this project will be finding a way to revisit this information going forward without doing the exact same presentation every year and that it will probably only reach those who go to the Diabetes Support Group. The PHN understands the vision for the presentation and active group discussion and it is scheduled to be implemented.

Global health II

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

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USING COMMUNITY ENGAGEMENT BASED STRATEGIES TO ADDRESS DENTAL DISEASE IN A RURAL HIMALAYAN BOARDING SCHOOL¹KR Suri*, ²MT Moor-Smith, ¹J Aleksejuniene, ²V Kapoor. ¹University of British Columbia, Burnaby, BC, Canada; ²University of British Columbia, Vancouver, BC, Canada

10.1136/jim-2017-000663.289

Purpose of study To identify contributing factors of dental disease and implement community-centred, sustainable interventions that promote oral self-care for students in a boarding school in the Indian Himalayas.

Methods used Perspectives and behaviours surrounding oral health were gathered through site observations and interviews of school personnel, students, community members and health care officials. Dental screening of all 486 students, from kindergarten to grade 10, assessed the students' oral hygiene practices, experience of dental pain, and the prevalence of dental caries. The overall results were shared with school personnel and student leaders to facilitate a discussion around designing and implementing interventions to improve the students' oral health.

Summary of results Of the students that were screened, 37% of students reported having a toothache and 62% had at least one advanced caries lesion. 68% of students had their own toothbrush, but only 19% of children brushed their teeth at least once a day. Easy access to cariogenic foods, lack of oral self-care routines, repeated loss of toothbrushes and limited knowledge about the importance of oral health were the major contributing factors to high caries prevalence. School personnel and student leaders designed and implemented: i) a storage and distribution system of donated toothbrushes and toothpastes, ii) daily tooth brushing routine for all children up to grade five iii) letters to students' parents to encourage routine tooth brushing at home iv) oral self-care instructions delivered by health council members and v) a student-led, creative video project that highlights the importance of good oral self-care.

Conclusions The director of the school identified dental caries among students as their most urgent health concern and committed support activities targeting its reduction over the coming years. The dental health promoting interventions designed jointly with community members were widely accepted, successfully implemented and their effectiveness will be evaluated next year.

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BASELINE ASSESSMENT OF MATERNAL-NEONATAL HEALTHCARE QUALITY IN LOKHIM, NEPAL¹J Doane*, ²A Sherpa, ¹SE Schoenhals, ²L Lama, ¹K Bjella, ¹A Chambers, ¹S Jacob, ¹R Malhotra, ¹B Fassl, ¹D Levy. ¹University of Utah School of Medicine, Salt Lake City, UT; ²Human Rights, Peace, Development Forum Nepal, Phaplu, Nepal

10.1136/jim-2017-000663.290

Purpose of study To determine the current quality and availability of maternal and child health (MCH) care in Lokhim VDC, Solukhumbu District, Nepal

Methods used In June 2017, we surveyed a convenience sample of 34 women at the Lokhim Health Post who had delivered in the previous 24 months. Women were identified through birthing records and by local community health workers from 7 local wards. Data were collected during household interviews using a standardised survey tool based on WHO criteria for MCH care. Surveys were administered using the EpiCollect5 mobile app.

Summary of results 25/34 (74%) mothers reported having a birth preparedness plan, and 31/34 (91%) had their blood pressure checked at least once during pregnancy. 5/34 (15%) of expecting mothers were screened for anaemia and 5/34 (15%) had a urinalysis. Of 34 live births in the Lokhim VDC, 28/34 (82%) were home deliveries. 3/34 (9%) births had all four elements of essential newborn care as defined by WHO (immediate drying and skin-to-skin placement, umbilical cord clamping delayed 1–3 min, and breastfeeding within 1 hour), and 3/34 (9%) neonates showed signs of sepsis after delivery. There was one maternal and one neonatal death in the preceding 12 months. 9/34 (26%) neonates had a health worker check within one week of birth, and 14/34 (41%) mothers reported receiving a health check within 6 weeks of delivery.

Conclusions There are significant gaps in MCH care in Lokhim VDC. Strengthening of MCH services is critical. Establishing a properly equipped birthing centre staffed by trained providers will help to improve the quality of care in Lokhim. Future postintervention measurements will allow for impact assessment.

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ENGAGING STAKEHOLDERS TO IMPLEMENT PERIPARTUM CARE QUALITY MEASURES AT A RURAL HOSPITAL IN GUJARAT, INDIA¹B Kemp*, ¹KA Bodily, ²M Patel, ²R Chovatiya, ¹B Fassl, ¹E Vandervort. ¹University of Utah, Salt Lake City, UT; ²C.A. Hospital, Mota Fofalia, India

10.1136/jim-2017-000663.291

Purpose of study Shifting births to facilities with skilled birth attendants (SBA) has not correlated with a significant decrease in India's maternal mortality rate (MMR). Evidence-based practices can reduce MMR and improve care quality. Ensuring participation of frontline health workers in quality improvement (QI) initiatives can lead to sustained system improvements and superior outcomes. This QI project seeks to improve maternal and neonatal care at the Mota Fofalia Community Health Centre in Gujarat, India.

Methods used Potential peripartum care quality measures were developed through a global literature review. A collaborative process was undertaken with local stakeholders: nurses, physicians and administrative staff. Individual interviews and four group meetings with five doctors; one OBGYN, hospital administration and eleven nurses were conducted over a non-consecutive seven-week period from June to August 2017. Using a modified Delphi approach, proposed quality measures were vetted for reliability, validity and feasibility in this setting.

Summary of results Hospital leadership reached a final consensus on 22 quality measures. Each stage of labour has five care measures. Four measures focus on neonatal care and three

describe postpartum care quality. Direct observations (n=24) were utilised to determine compliance with the proposed measures and WHO care standards. Among observed births, 96% (23/24) of women received antenatal care and 100% of women were accompanied during the first stage of labour. However, many care gaps were identified. Partographs were not utilised for any women (0/24) during the labour process. At least 46% (11/24) of women did not have their blood pressure evaluated on admission and only one patient (1/24) had vital signs measured in the postpartum period. At least 54% (13/24) of women underwent routine episiotomies and only 8% (2/24) of fetal heart tones were obtained during second stage.

Conclusions Adherence to evidence-based birth practices is low at this site. Significant investment is required to ensure that frontline SBAs are truly skilled, thus leading to improved care quality. Implementation of a peripartum QI program is urgently needed. The impact of these efforts will be tracked using the 22 quality measures.

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ASSESSING OPPORTUNITIES FOR IMPROVED MATERNAL-NEWBORN HEALTH IN SOLUKHUMBU, NEPAL

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10.1136/jim-2017-000663.292

Purpose of study Improving maternal-newborn health is a global priority. Rural Nepal has a neonatal and maternal mortality rate well above the WHO's 2030 target. The purpose of this study is to obtain baseline data about maternal-neonatal care capacity of health facilities and baseline health outcomes in Solukhumbu District, a remote, mountainous area of Nepal to identify opportunities for improving care delivery.

Methods used Between February 2015 and December 2016 we conducted on-site evaluations of health facilities throughout Solukhumbu. Surveyors included medical personnel from University of Utah and a Nepal-based NGO. The facility survey, developed by Health Rights International, has been validated for assessing health facilities in the developing world. Data were analysed for major gaps and areas for improvement. Maternal-neonatal outcomes data were abstracted from existing patient records.

Summary of results We surveyed 19 facilities, including 2 hospitals, 3 primary health care centres, 11 health posts, and 3 sub-health posts. Basic health infrastructure: 84% (16/19) had electricity and 79% (15/19) had running water. One facility had oxygen. Staffing and services: 89% (17/19) had at least one auxiliary nurse midwife, although not all were trained skilled birth attendants. 79% (15/19) reported insufficient staff and/or training. All provided antenatal care, 58% (11/19) provided routine delivery care, and 95% (18/19) provided postnatal care. Deliveries were reported at 53% (10/19) of facilities. Of those, 90% (9/10) were equipped with a bag and mask. 30% (3/10) reported use of a partograph and 80% (8/10) used oxytocin in the 3rd stage of labour. Immediate drying of the newborn and breast-feeding in the first hour were reported by 90% (9/10). Maternal-neonatal outcomes: Of 388 recorded deliveries, there were 16 stillbirths and 15 neonatal deaths, 53% (8/15) of which were home births. There were 2 maternal deaths, one of which was at home.

Conclusions There are many opportunities to improve maternal-newborn care and perinatal outcomes in Solukhumbu. These include a program to track home births, encourage facility deliveries, and improve access to birthing centres with trained staff and proper equipment.

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ASSESSMENT OF MATERNAL-NEWBORN CARE DELIVERY IN SOLUKHUMBU NEPAL

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10.1136/jim-2017-000663.293

Purpose of study Most infant deaths globally occur in developing nations such as Nepal and are commonly associated with limited prenatal care, inadequate intrapartum care, and lack of postnatal care visits. Little information exists about the quality, availability, and utilisation of maternal-neonatal care in Solukhumbu District, Nepal. The objective of the study was to obtain baseline, pre-intervention data on maternal and newborn antenatal, intrapartum, and postpartum care quality and practices and outcomes in Solukhumbu.

Methods used The study took place in 8 geographically separated areas (VDC) of Solukhumbu. We identified and surveyed women in local birth records who had delivered in the preceding 24 months. The survey was based on the 'Consultation on Improving measurement of the quality of maternal, newborn, and child care in health facilities' reporting tool from the WHO and reports on evidence based interventions in the antenatal, intrapartum, and postnatal periods. The study was approved by the Nepal Ministry of Health and the University of Utah IRB.

Summary of results We surveyed 337 women in 8 VDC; 1 maternal death and 1 infant death were reported. Maternal care: 70% (237/337) had a birth preparedness plan, 49% (166/337) were screened for anaemia, 85% (285/337) had blood pressure checks, and 35% (102/294) received oxytocin. Intrapartum care: 22% (67/302) of deliveries had resuscitation equipment available, 63% (213/337) of deliveries occurred in a health facility (hospital or birthing centre) and were attended by a skilled birth attendant. Complications occurred in 16% (55/337) of deliveries (bleeding, prolonged labour). 25% (80/326) were attended by an SBA with training in neonatal resuscitation. Among low birth weight infants (<2500 g), 6% (6/107) were appropriately identified and 7% (24/336) had danger signs. Essential newborn care in live births: 75% (248/332) were immediately dried, 18% (59/334) were placed skin-to-skin, 44% (145/332) had delayed cord clamping, and 73% (243/335) were breastfed within the first hour. 65% (219/337) received postnatal follow up within 6 weeks.

Conclusions There are significant gaps in maternal and infant care. Interventions to improve services are urgently needed.

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ANALYSIS OF THE PREVALENCE OF HELICOBACTER PYLORI IN BASAN GRANDE: A MEDICALLY UNDERSERVED COMMUNITY IN ECUADOR

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10.1136/jim-2017-000663.294

Purpose of study The aim of this study is to determine the prevalence of *Helicobacter pylori* (*H. pylori*) in Basan Grande, a medically underserved rural community in Ecuador, which is widely representative of the types of rural communities in Ecuador that have little to no access to health care or clean water and sanitation systems.

Methods used This pilot study is an observational, cross-sectional analysis of the prevalence of *Helicobacter pylori* among residents of Basan Grande, Ecuador. An *H. pylori* blood-antibody test was administered to consenting participants via a capillary stick to obtain a positive or negative result. Participants included residents of Basan Grande, in the Chimborazo Province of Ecuador, who visited the free medical clinic and provided appropriate consent. Consenting residents of all ages from Basan Grande were included. Patients residing outside the Chimborazo Province were excluded from this study. Descriptive statistics were run on collected data.

Summary of results This study showed that the prevalence of *Helicobacter pylori* was 59% among the residents of Basan Grande, Ecuador. *H. pylori* was prevalent in 60.5% of female participants and 57.8% of male participants. *H. pylori* had the highest prevalence in participants ages 26–50 years of age (67.4%) and was lowest in participants ages 76–100 (11.1%). Stomach pain was a chief complaint in 25.6% of participants (95% CI: 19.7% to 32.4%).

Conclusions Notably, *Helicobacter pylori* is prevalent in 59% of tested residents in rural Basan Grande, Ecuador. Determining a causal relationship between *H. pylori* and the chief complaint of 'stomach pain' requires further future investigative studies. Programs directed at water sanitation are necessary in order to treat the underlying source of *H. pylori* infection.

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CURBING ALCOHOL ABUSE AND ITS SEQUELAE IN NEPAL THROUGH A MULTI-FACETED EDUCATIONAL CAMPAIGN

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10.1136/jim-2017-000663.295

Purpose of study Cirrhosis is the 12th leading cause of death in Nepal with 75% being attributed to alcohol abuse. 1 in 5 adults at Dhulikhel Hospital (DH) die from it. Alcohol abuse further contributes to morbidity and mortality by perpetuating poverty, causing road traffic accidents, and increasing risk for injury, self-harm, violence, and other diseases. Government efforts to quash the growing burden of alcohol abuse and its sequelae have been unsuccessful as they have neglected community education. The goal of this project was to remedy this: to provide teaching materials on the harmful effects of alcohol.

Methods used Local attitudes and trends in alcohol consumption were assessed through interviews with patients admitted to DH with alcoholic liver disease (ALD) or withdrawal symptoms, a visit to a home raksi distillery, informal conversations, and direct observation. A literature review of government reports, demographic surveys, and studies of Nepali cultural practices served as complement. Materials were developed based on published guidelines in consideration of the above information, reviewed in collaboration with local nurse educators, nutritionists, and community health partners for cultural relevance, and approved by DH hepatobiliary consultants.

Summary of results Three posters (demonstrating ALD progression, promoting symptom recognition and early intervention, and depicting decompensated cirrhosis) were created to post at DH and its 18 affiliated community clinics to increase ALD awareness. Two brochures (ALD and cirrhosis) and one PowerPoint were developed to improve patient education in the hospital/clinic setting. An addiction counselling guide and alcohol cessation toolkit were drafted for nurse educators and patients, respectively. An interactive PowerPoint presentation targeted to adolescents on the harmful effects of alcohol and healthy drinking habits was piloted at a nearby school; 83% of the 120 8th–10th graders reported being less likely to abuse alcohol when polled one week later.

Conclusions Materials are being translated and, pending final approval, will be printed and distributed as above. The PowerPoint will serve as a foundation for ALD and Cirrhosis patient group counselling starting October 2017. My community partners will provide updates on the impact of these materials as they are implemented.

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STRENGTHS AND RESILIENCY FACTORS AMONG REFUGEES IN METRO VANCOUVER: A PARTICIPATORY APPROACH

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10.1136/jim-2017-000663.296

Purpose of study There is a lack of research on refugees that focuses on identifying factors that can empower refugees to take control of their own resettlement. Furthermore, little longitudinal research exists about refugee resettlement that assesses which factors lead to future success. This study aims to identify the resiliency factors and strengths among a diverse group of newly-settled refugees in Metro Vancouver during resettlement, and compare these to the resiliency factors and strengths utilised by refugees who have been settled in Canada for 5 or more years.

Methods used Key informant interviews will be conducted with members of community organisations that aid refugees in Metro Vancouver (e.g. settlement organisations, healthcare workers). Semi-structured individual interviews will be conducted with newly-arrived refugees and settled refugees to explore strengths and resiliency factors during resettlement. After the data from interviews has been transcribed and coded, secondary interviews will be conducted with the participants to discuss the themes that were generated, and identify how these findings can be translated to empower the refugee population.

Summary of results Initial data analysis from key informants has uncovered many consistent themes involving refugee strengths and resiliency factors. Of note are strengths such as language skills, meaningful employment, and building social connexions, as well as resiliency factors such as religion and spirituality, family unit, and gratefulness. All of these aspects assist these refugees with their health and resettlement as they navigate their new environment. Continued data analysis (still underway) from interviews with new and settled refugees will uncover more themes that can be compared to this data from key informants.

Conclusions By emphasising the inherent resiliency factors and strengths of refugees that have been consistent across new and

settled refugees, we plan to shed light on how these strengths can be leveraged to enhance refugee resettlement. The participatory nature of this project will help to inform organisations that help refugees, and empower refugees themselves, to build upon the refugee community's strengths and resiliency.

297 HAND HYGIENE EDUCATION CAMPAIGN AT SOROTI REGIONAL REFERRAL HOSPITAL, UGANDA

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10.1136/jim-2017-000663.297

Purpose of study Previous research done at Soroti Regional Referral Hospital (SRRH) identified that health care providers recognise the importance of hand hygiene, and despite this the compliance is still low. This project was an implementation of a WHO hand hygiene campaign at SRRH during May 2017. Our objective in the long term is to improve overall hand hygiene compliance and knowledge at SRRH; and in the short term to provide hand hygiene education and assess compliance in health care professionals.

Methods used This campaign consisted of 3 parts: 1) Pre-intervention – observation of hand hygiene according to WHO observation surveys in 9 areas of SRRH; calculation of compliance (%) for physicians and nurses. 2) Workshops – education to physicians and head nurses on hand hygiene steps and the 'Five Moments of Hand Hygiene' were conducted over 5 sessions. 3) Post-intervention – observation of hand hygiene following similar methods as pre-intervention; discussion among stakeholders on barriers to hand hygiene.

Summary of results Compliance rate pre-intervention was 15.7% (nurses 9.1%, physicians 28.6%). Compliance rate post-intervention was 19.7% (nurses 5.9%, physicians 28.8%). Hand sanitizer and education materials were provided to the staff during our education sessions; workplace reminders such as posters and stickers were also implemented. Some points brought up during stakeholder discussion included: lack of resources, transmission of micro-organisms, and lack of means to ensure that hand hygiene steps are followed appropriately.

Conclusions This project demonstrated the feasibility of implementing a WHO campaign at SRRH. Overall compliance rate did show slight improvement post-intervention, but there were limitations due to the small size of this project. However, we noted that there are still gaps in hand hygiene at SRRH and that there is significant need for infection control improvement.

Health care research II

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

298 UNDERSTANDING THE JOURNEY TO CARE FOR UGANDAN CHILDREN WITH RARE SURGICAL DISEASES

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10.1136/jim-2017-000663.298

Purpose of study To describe the current state of the referral system for children with rare surgical diseases at two referral hospitals in Uganda.

Methods used This study in Uganda was completed at two hospitals, Mulago National Referral Hospital in Kampala, which serves the whole country and Soroti Regional Referral Hospital in Soroti, a smaller rural community serving a large eastern regional catchment. The study was conducted from April to June 2017. The two arms of the study were: a patient questionnaire and a focus group discussion concerning current and best practices of referral and care for these children. The list of rare surgical diseases considered for this study have incidences of less than 5 per 10 000 live births and was compiled by paediatric surgeons experienced in the Uganda setting.

Summary of results A total of 70 patient families (55 from Kampala, 15 from Soroti) and 24 health care professionals (9 from Kampala, 15 from Soroti) participated in the study. From the patient questionnaire, the two most commonly reported diagnoses were anorectal malformation and Hirschsprung's disease. The median time elapsed between the presentation of the first symptom and the final diagnosis ranged from 0 to 120 days. Furthermore, about 93% of diagnoses were delivered in person and the majority were well-delivered and accompanied by psychological support. Although both hospitals in this study are government hospitals and theoretically offer free treatment and tests, 70% of study respondents at both hospitals paid out of pocket for medical tests. The focus group responses at both hospitals suggest that the greatest challenges in referring patients with rare surgical diseases are in transportation and financial constraints whereas the greatest challenge in receiving referrals is lack of supportive manpower.

Conclusions While the majority of respondents received a well-delivered in-person diagnosis, financial barriers present significant hardships whereby patients may struggle to pay for government hospital care and transportation for referral.

299 ABSTRACT WITHDRAWN

300 ALASKA NATIVE ELDERS' SUCCESSFUL AGEING AND RURAL HEALTHCARE

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10.1136/jim-2017-000663.300

Purpose of study This study attempts to understand healthcare's effect on successful ageing within Alaska Native Elders and how their views and experiences with the healthcare system affects their motivation and/or willingness to seek care.

Methods used Qualitative data was gathered in the form of semi-structured interviews with nominated Alaska Native Elders in 5 communities within the Norton Sound southern sub-region of Northwest Alaska. A total of 41 Alaska Natives Elders were interviewed. The study participants were nominated by the respective village councils in each participating community. Elders were nominated based on the community's respect of them as Elders despite their health status, cultural practices, etc. Interviews lasted approximately 35 min. The interviews were recorded, transcribed, and analysed for themes using qualitative analysis software.

Summary of results Elders were pleased with the healthcare services available and praised the providers. Physical health plays a critical role in healthy ageing, especially when it limits mobility. Elders are pleased with advances in rural medical services and report being happy with the care provided. However, themes were identified that highlighted Elders' decreased satisfaction and utilisation of healthcare services. They included: lack of communication with providers, lack of explanation regarding the policies/procedures of the healthcare system, lack of follow-up care, decreased sense of local representation and voice in healthcare, and unexplained prolonged wait times for services.

Conclusions Elders voiced concerns about communication breakdown and lack of understanding of health care system.

Without proper explanations, Elders were left to come up with their own rationales on how healthcare decisions were made. There was widespread support of the clinics and the providers by the Elder population. One area of possible improvement would be to improve the communication and transparency from the clinic and hospitals regarding services offered, medevac decisions, health care decisions, and policies. This would help alleviate the ambiguity of medical care and increase patient satisfaction. These efforts would also increase the clinics relationship with the community and help alleviate barriers in healthcare treatment, which would support Elders to age successfully.

301 LOW VACCINE AWARENESS AMONG SPANISH-SPEAKERS MAY EXPLAIN HIGH RATE OF WHOOPING COUGH INFECTION AMONG HISPANIC NEWBORNS

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10.1136/jim-2017-000663.301

Purpose of study Hispanic populations are disproportionately affected by whooping cough epidemics in California. To reduce newborn infection, the Centre for Disease Control recommends Tdap vaccination for the mother and close contacts. This study seeks to determine the level of Tdap awareness, anticipated vaccine coverage, and attitudes toward Tdap among Hispanic and non-Hispanic, as well as English- and Spanish-speaking groups.

Methods used Pregnant women and their male partners were invited to participate in a private oral survey in English or Spanish at a prenatal clinic serving a primarily indigent population. Results were considered significance when Chi square test resulted in $p < 0.05$. IRB approval was granted by LABioMed and Western University.

Summary of results 311 total surveys were analysed, of which 263 were from English speakers. English speakers were significantly more aware of Tdap than Spanish speakers ($p < 0.001$), with 48% and 15% awareness, respectively. There was no significant impact of Hispanic vs non-Hispanic ethnicity on Tdap awareness ($p = 0.07$), where 39% of Hispanics and 49% of non-Hispanics were aware of Tdap. Hispanic English-speakers were significantly more aware of Tdap than Hispanic Spanish-speakers ($p = 0.01$), with 47% and 15% awareness, respectively. Of 133 respondents who reported hearing of Tdap, 60%

Abstract 301 Table 1 Tdap awareness and coverage by language and ethnicity

	English		Spanish		Hispanic		Non-hispanic					
	% Aware	% Coverage	% Aware	% Coverage	% Aware	% Coverage	% Aware	% Coverage				
Female	159	62%	34%	25	24%	20%	112	50%	32%	72	67%	32%
Male	104	27%	16%	23	4%	0%	79	23%	15%	48	23%	10%
Total	263	48%	27%	48	15%	10%	191	39%	25%	120	49%	23%

% Coverage = % already received Tdap or planning to get Tdap before the baby is born.

believed it's important for family members to get. Among the 107 respondents aware of and not previously vaccinated with Tdap, only 20% did not intend to get Tdap before the baby was born.

Conclusions Being English- or Spanish-speaking is a stronger determinant of Tdap awareness than Hispanic or non-Hispanic ethnicity. Raising awareness of Tdap among Spanish-speaking populations may increase uptake and reduce the incidence of newborn whooping cough infections in California.

302 IDENTIFYING FACTORS CONTRIBUTING TO NOSOCOMIAL INFECTIONS IN A NEONATAL UNIT IN BUTARE, RWANDA

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10.1136/jim-2017-000663.302

Purpose of study Health care associated infection (HCAI) outbreaks with multi-drug resistant *Klebsiella Pneumoniae* (KP) are a significant problem in many neonatal units in sub-Saharan Africa. The purpose of this study is to describe staff adherence to hygiene standards outlined by WHO and to report on the number of KP cases before introduction of a standardised hygiene protocol.

Methods used The quality improvement study took place at the University Teaching Hospital of Butare, Rwanda (CHUB). Hygiene practices of nursing staff, medical students, residents, paediatricians, and family members in the neonatal unit at CHUB were observed at random times in March 2017. Using a standardised checklist, their actions were recorded on the 5 moments for hand hygiene according to the WHO (before and after patient contact, before aseptic procedure, after body fluid exposure, after touching patient surroundings) and

cleaning of equipment before and after use. The number of KP cases confirmed by blood culture were obtained from records kept by the head nurse in neonatology.

Summary of results A total of 186 hygiene observations were completed. Handwashing or hand sanitizer was recorded as being performed for only 36.0% of the opportunities observed. Equipment such as stethoscopes, thermometers, and oxygen saturation probes were sanitised only 44.0% of the time. Nursing staff and physicians did not perform hand hygiene for 57.6% and 42.9% of the opportunities, respectively. From November 2016 to February 2017, 42 cases of confirmed KP sepsis in a total of 389 admissions to the neonatal unit and 110 total all cause deaths were reported. Rates of confirmed KP cases per month ranged from 2.0% to 26.9% with an average of 11.1%.

Conclusions KP HCAI represent a significant problem in this referral hospital. Poor hand hygiene and infrequent sanitation of materials are major contributing factors. A multidisciplinary approach to improving hygiene practices including training sessions for all staff and regular cleaning of all surfaces may reduce HCAI in this neonatal unit.

303 DEMENTIA MORTALITY IN ALASKA

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10.1136/jim-2017-000663.303

Purpose of study Dementia is a significant source of mortality in the United States. In the period 1999–2015, the dementia mortality rate in Alaska has increased and is higher than the national average. The greatest risk factor for increasing dementia incidence is an older population, but the median age in Alaska is, on average, 3.1 years younger than the national median age. We examine and compare the Alaskan and national dementia mortality rates.

Abstract 303 Figure 1 'Unspecified dementia' age-adjusted mortality rates: Alaska and national, 1999–2015

Methods used The mortality rates due to 'Unspecified dementia' and 'Alzheimer's disease, unspecified' for Alaska and the United States for years 1999–2015 were obtained from CDC WONDER and analysed. Population data were obtained from the US Census Bureau. All mortality rates are age-adjusted to the 2000 Standard US Population.

Summary of results In the years 1999–2015, the Alaskan mortality rate for 'Unspecified dementia' has increased from 16.1 (95% CI: 10.7 to 23.3) to 37.8 (95% CI: 31.8 to 43.8) deaths/100,000 population, while the national rate increased from 10.4 (95% CI: 10.3 to 10.5) to 28.4 (95% CI: 28.3 to 28.6). The Alaskan 'Unspecified dementia' mortality rate was higher than the national average in 16 of 17 years of analysis. However, in the same period, the Alaskan mortality rate for 'Alzheimer's Disease, unspecified' has remained relatively stable while the national rate has markedly increased.

Conclusions Dementia mortality is a burden on the Alaskan and national populations. The Alaskan mortality rate due to 'Unspecified dementia' is higher than the national average in 16 of 17 years of the most recent available data. The national Alzheimer's disease mortality rate has increased more rapidly than the Alaskan rate. Public awareness of the mortality associated with dementia, and disease-delaying and -preventing measures as well as dementia-specific care should be advocated for at the state and national levels.

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A FOLLOW-UP ASSESSMENT OF SICKLE CELL DISEASE AND ITS SCREENING PROGRAM IN THE INDIGENOUS THARU POPULATION OF NEPAL

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10.1136/jim-2017-000663.304

Purpose of study Sickle cell disease (SCD) is an inherited blood disorder commonly found in regions with endemic malaria and associated with significant morbidity and mortality. Between July 2015 and June 2017, a total of 3711 Tharu individuals located in the rural district of Dang in Western Nepal have been screened for SCD. Of these participants, 354 screened positive, six of whom were homozygous for the disease. Through the use of focus groups, this study followed up with those who underwent the screening and/or diagnosis process to evaluate the effectiveness of the program and to better characterise the health and socioeconomic barriers that members of the Tharu community face.

Methods used A qualitative study with 134 participants was completed through 22 focus groups. Each focus group comprised of six to eight participants and a translator. Participants' audio responses were recorded in Nepali and Tharu (the local dialect) and later translated into English. Questions explored participants' knowledge and ideas about SCD, their perception of the screening and diagnosis program, and barriers to treatment access.

Summary of results Analysis from the focus group discussions identified several major themes regarding SCD and its impact on the community. The major themes regarding SCD include lack of knowledge about the disease's mode of transmission and its aetiology, eagerness to learn from healthcare workers, and interest in gaining more information about the disease through interactive sessions such as forum theatres or discussion groups. The themes with respect to the screening/diagnosis process included fear of having blood drawn, difficulty making time to travel for the tests, and strong desire to know one's disease status.

Conclusions SCD remains a problematic health concern for the Tharu community. Future directions include working to develop nationwide screening at infancy in high risk populations, increasing accessibility of diagnostic testing, and continuing to educate community members about SCD aetiology, diagnosis, and treatment. The qualitative data collected, along with prior quantitative results, has laid the foundation for our cohort to guide future directions for the project.

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ASSOCIATION BETWEEN MATERNAL SERIOUS MENTAL ILLNESS AND ADVERSE BIRTH OUTCOMES

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10.1136/jim-2017-000663.305

Purpose of study Women with serious mental illness (SMI) during pregnancy are at an increased risk for adverse birth outcomes. However, no previous study has disentangled the direct effects of SMI on a wide range of birth outcomes from the presence of confounding risk factors associated with SMI. This study estimates the effect of SMI on adverse birth outcomes controlling for a wide variety of these confounding risk factors.

Methods used This was a retrospective study using the Healthcare Cost and Utilisation Project's National Inpatient Sample with 20% of discharges from participating hospitals in the U. S. from 2008 to 2014. We identified the prevalence of ten risk factors associated with adverse birth outcomes (anaemia, diabetes, infections, obesity, thyroid dysfunction, epilepsy, malposition/malpresentation of the fetus, and tobacco, drug, or alcohol abuse) and a diagnosis of SMI (major depressive disorder, bipolar disorder, and/or schizophrenia) from the maternal records of all births for mothers aged 10 or older. We report relative risk (RR) of adverse gestational, obstetric and fetal outcomes in women with SMI, using multivariable logistic regression to adjust for hospital/patient characteristics (race, age, payer, urban/rural, U.S. region, income, year, and weekend, elective, or emergency department admission) and the aforementioned risk factors.

Summary of results Our sample includes more than 5 million births, 43 042 of which had a recorded maternal SMI (7.8 per 1000 births). The unadjusted relative risk of adverse birth outcomes was increased for women with SMI. Adjusting for

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hospital/patient characteristics and risk factors reduced the relative risk, but it remained significantly elevated for all three outcomes (table 1).

Conclusions Addressing SMI-associated risk factors prior to or during pregnancy and child birth, and increasing awareness of maternal SMI in clinical settings may reduce the occurrence of adverse birth outcomes in this at-risk population.

Abstract 305 Table 1 Risk of adverse birth outcomes in women with a diagnosis of SMI

	No SMI (n=5,500,613)	Any SMI (n=43,042)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Adverse gestational outcomes	25.9%	30.7%	1.18 (1.17–1.20)	1.08 (1.06–1.09)
Adverse obstetric outcomes	43.0%	46.3%	1.08 (1.06–1.09)	1.03 (1.02–1.05)
Adverse fetal outcomes	21.5%	27.3%	1.27 (1.25–1.29)	1.12 (1.10–1.14)

306 TRENDS IN INCIDENCE AND CHARACTERISTICS OF PAEDIATRIC PATIENTS WITH NON-ACCIDENT TRAUMA IN THE UNITED STATES

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10.1136/jim-2017-000663.306

Purpose of study Intentional injuries play a major role in child mortality and morbidity worldwide. There is a dearth of literature looking at trends in the incidence and outcomes of non-accidental trauma (NAT) amongst children, based on nationwide data from the United States (US). Our aim was to study the current epidemiology and socioeconomic factors associated with incidence and outcomes of NAT amongst children in the US.

Methods used We used the Nationwide Inpatient Sample, a discharge database representative of all short-term, nonfederal hospitals in the United States. Paediatric patients were identified using the age cutoff of 18 years. International Classification of Diseases (ICD 9) codes for NAT were used to identify patients discharged with a primary diagnosis of NAT. Trends in the incidence and outcomes of paediatric NAT were compared for different age groups, gender, race and socioeconomic status (SES) based on quartiles (Qx) of median household income.

Summary of results In 2013 to 2014 there were a total of about 2–3 million paediatric discharges per quartile. Out of these a total of 8985 had a primary diagnosis of NAT. Incidence was 109.1 per 1 00 000 discharges in the lowest SES (Q1) compared to 33.1 in Q4. This trend was consistent across all studied age groups and ethnicities. In-hospital mortality was 2.4% in Q1 compared to 0.4% in Q4.

Conclusions Children from low SES households have a higher incidence of NAT and have significantly higher in-hospital mortality. This trend is consistent across all age groups and ethnicities.

Haematology and oncology II

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

307 CHARACTERISATION OF NASOPHARYNGEAL CARCINOMA IN ALASKA NATIVE PEOPLE

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10.1136/jim-2017-000663.307

Abstract 306 Figure 1 Incidence and in-hospital mortality of NAT. (*incidence per 100,000 discharges, **in-hospital mortality rate as percentage)

Purpose of study Nasopharyngeal carcinoma (NPC) is a rare form of cancer in the United States with an incidence of less than one case per 1 00 000 people each year. Geographic variations of incidence of NPC provide an interesting investigation into the environmental factors, genetic components and role of Epstein-Barr virus (EBV) in the aetiology of this cancer. In the Alaska Native population NPC has an incidence and mortality rate 17.3 and 20.1 times greater, respectively, than in the U.S. white population. Rates of NPC also range widely across the state with a six-fold difference between certain regions. Through a systematic chart review, we evaluated the aetiology of NPC to better characterise this cancer and treatment in the Alaska Native people.

Methods used Between 1976 and 2016 we identified 180 cases of NPC using the Alaska Native Tumour Registry and Alaska Native Medical Centre Tumour Registry and extracted data for analysis. A systematic chart review was performed for each case to extract further data needed for analysis.

Summary of results The median age at diagnosis was 60 years with 68% of patients being male. The World Health Organisation classifications were 26% Type 1, 16% Type 2, and 58% Type 3 tumours. The percentage of WHO Type 3 tumours varied by region and increased with prevalence of NPC. The southwest region had the most cases of NPC (n=52) and highest percentage of Type 3 tumours at (67%). AJCC TNM staging percentages of the total population (n=180) ranged from 2% diagnosed at stage I, 10% at stage II, 9% at stage III, and 43% at stage IV, with staging data not available for all cases. The median survival of all patients was 2.5 years (95% Confidence Interval 1.52–3).

Conclusions NPC in the Alaska Native population has both a poor prognosis and survival. As WHO Type 3 tumours are associated with EBV, the increasing rate of Type 3 tumours in areas with the highest prevalence alludes to the role EBV may play in the geographical distribution of cases across the state. Further analysis of tumour specimens identified during this project could provide definitive evidence of the contributions EBV makes to distribution of NPC among the Alaska Native population.

308 PHASE I DOSE ESCALATION OF INTRAPERITONEAL DENILEUKIN DIFTITOX FOR ADVANCED STAGE OVARIAN CANCER

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10.1136/jim-2017-000663.308

Purpose of study Regulatory T cells (Tregs), which induce T cell suppression, are increased in the ascites and peripheral blood of ovarian cancer patients and associated with a poor prognosis. Tregs in the peritoneum suppress immune-mediated tumour destruction and therefore depletion of these Tregs could restore antitumor immunity. We questioned whether intraperitoneal (I.P.) infusion of denileukin diftitox, a diphtheria/IL-2R fusion protein, was safe, able to reverse immune suppression in the peritoneum, and able to alter the clinical progression of ovarian cancer.

Methods used The study was a phase I, non-randomised, dose escalation study of I.P. denileukin diftitox administration in 10 patients with advanced, refractory ovarian carcinoma. 3 dose levels of the drug were investigated (5 µg/kg, 15 µg/kg, 25 µg/kg) and the Cancer Therapy Evaluation Program, Common

Terminology Criteria for Adverse Events (CTEP CTCAE) was used to assess the drug's safety. Tregs were quantified using flow cytometry, clinical impact was assessed using serial CA-125 measurements, and circulating cytokines were assessed using standard ELISA kits.

Summary of results Treatment with I.P. denileukin diftitox was well tolerated between 5–15 µg/kg with the majority of adverse events being transient grade 1–2 hypoalbuminemia. No dose-limited toxicities (DLTs) were seen in patients treated with 5 µg/kg, however DLTs were seen at both 15 µg/kg and 25 µg/kg of treatment. Additionally, patients treated with 5 µg/kg and 15 µg/kg showed a significant decrease in Tregs in peripheral blood but not in ascites. The majority of treated patients maintained stable disease and patients treated at 15 µg/kg showed improved disease stabilisation than those treated at 5 µg/kg. Treated patients did not show any significant changes in cytokine levels.

Conclusions Denileukin diftitox can be delivered I.P. between 5 and 15 µg/kg with an acceptable toxicity profile. Patients treated with 5 and 15 µg/kg of denileukin diftitox showed disease stabilisation based on CA-125 response. I.P. denileukin diftitox at both 5 µg/kg and 15 µg/kg results in decreased Tregs in the peripheral blood, but not in ascites, suggesting that the drug may have the ability to augment tumour antigen-specific immunity and promote tumour regression.

309 IMMUNE-RELATED ADVERSE EVENTS WITH IPILIMUMAB TREATMENT OF ADVANCED MELANOMA: A SINGLE INSTITUTION EXPERIENCE

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10.1136/jim-2017-000663.309

Purpose of study Immune checkpoint therapy is the mainstay for melanoma treatment. A complete understanding of immune-related adverse effects (irAEs) is critical in reducing morbidity and mortality from immunotherapy and improving overall patient outcomes. The purpose of this study is to evaluate the immune-mediated side effect profile of the anti-CTLA4 antibody, ipilimumab, in patients treated for melanoma at the University of Arizona Cancer Centre.

Methods used After IRB approval, the Banner University Medical Centre database was queried for patients with stage III-IV melanoma treated with ipilimumab between 2011 and 2017. Demographics, treatment regimen, irAEs and associated hospitalizations and lab parameters were obtained. Side effects were graded using the common terminology criteria for adverse events v.4.0 (CTCAE).

Summary of results 45 patients were identified; 11 had stage III and 34 had stage IV melanoma. The median number of cycles for stage III patients was 5 and stage IV was 4. In total, 93 irAEs were reported and 40/45 (88.9%) patients reported an irAE. Of the 93 irAEs, 55 (59%) were grade 1, 23 (25%) were grade 2, 14 (15%) were grade 3 and 1 (1%) was grade 4. The most common irAEs included: rash (44% patients, 21% of irAEs), pruritis (44% patients, 21% of irAEs), autoimmune colitis (22.2% patients, 10.7% of irAEs) and diarrhoea (17.8% patients, 8.6% of irAEs). Ten patients were hospitalised due to an irAE and 11 patients (24%) stopped immunotherapy completely due to an irAE. Autoimmune colitis was the most common grade 3–4 irAE and

contributed to 5 of the hospitalizations and 6 of the treatment cessations. Endocrinopathies such as adrenal insufficiency and hypophysitis were the second most reported grade 3–4 irAEs and constituted 4 of the hospitalizations and 4 treatment cessations. Of the 93 reported irAEs, 42 (45.2%) were treated with steroids (22 with topical steroids, 20 with oral steroids). No treatment related mortality was seen.

Conclusions The irAE profile of ipilimumab therapy at our institution mirrors the findings in landmark phase 3 trials. Immune-related adverse events were manageable and did not result in mortality. Early identification and proper management is critical in preventing serious treatment related adverse effects.

310 SERUM FERRITIN LEVELS IN PAEDIATRIC ONCOLOGY PATIENTS POST-CHEMOTHERAPY

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10.1136/jim-2017-000663.310

Purpose of study Iron overload (IO) is a long-term complication among cancer survivors who received multiple transfusions during treatment. The absence of indications for a routine screening test among post cancer treatment patients lead to unrecognised cases of IO in this population. This study examined the relationship between chemotherapy treatment characteristics and ferritin levels after chemotherapy.

Methods used The study included 27 cancer patients post chemotherapy (mean $\pm$ standard deviation for age was 7.6 ± 6.2 years; 12 patients were female (44%) and 15 (56%) were male). The study was conducted at the St. Joseph's Hospital, Department of Haematology and Oncology Clinic from March 2016 to March 2017. Patient information such as duration of treatment, cancer diagnosis, BSA, total transfused volume; number of transfusion, and average transfusion volume were correlated with serum ferritin levels.

Summary of results Only total transfused volume and number of transfusions were significantly ($p < 0.01$) correlated with ferritin levels ($r = 0.60$ and 0.68 , respectively). Regression analysis revealed that total transfused volume and number of transfusions can significantly predict ferritin levels, partialling out the influence of time; $F(2,26) = 5.86$, $p < 0.01$. Structure coefficients revealed that both measures significantly ($p < 0.01$) contributed to predicting ferritin levels.

Abstract 310 Table 1 Means, standard deviations of measured variables. Correlation coefficients and significance levels between ferritin levels and other measured variables. * = significant relationship with ferritin levels, $\alpha = 0.05$

	Mean $\pm$ SD	r value	p value
Ferritin levels (ng/mL)	435.9 $\pm$ 648.6	N.A.	N.A.
Change in BSA (m ²)	0.1 $\pm$ 0.1	−0.01	0.48
Number of transfusions	8.0 $\pm$ 7.2	0.68 *	<0.01
Total Transfused Volume (mL)	2972.5 $\pm$ 3286.0	0.60*	<0.01
Average Volume per Transfusion (mL)	288.9 $\pm$ 194.0	0.22	0.14
Duration of Treatment (days)	22.1 $\pm$ 12.9	0.13	0.26
Time b/w end of treatment and ferritin measurement (days)	307.3 $\pm$ 333.2	0.32*	0.04

Conclusions Results of this study support the need for formulating guidelines that will classify paediatric oncology patients into low or high-risk categories for iron overload based on the total transfused volume and number of PRBC transfusions during treatment.

311 FOLLOW-UP ASSESSMENT OF ANAEMIA PREVALENCE IN CHILDREN LIVING IN THE INDIAN HIMALAYAS

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10.1136/jim-2017-000663.311

Purpose of study Since 2007, the University of British Columbia has partnered with Munsel-ling Boarding School for Children to provide a health program servicing a rural, remote community in the Indian Himalayas. Initial annual testing revealed a high prevalence of anaemia within this population, and subsequent actions such as iron supplementation, health education, dietary changes, deworming, water sanitation, and greenhouses were implemented. This study aims to reassess anaemia prevalence using haemoglobin levels as a primary outcome.

Methods used 486 consenting students from ages 7–19 were tested using a HemoCue Haemoglobin Hb 201+Analyzer. Haemoglobin levels were collected during annual comprehensive health screens that included screening for dermatological, auditory, optical, dental, respiratory, cardiac, and gastrointestinal pathologies. Anaemia was adjusted for age, sex, and altitude. Mild anaemia was classified as haemoglobin levels less than 145 g/L for ages 7–11 years, less than 150 g/L for ages 12–14, less than 150 g/L for females over 15, and less than 160 g/L for males over 15.

Summary of results Based on World Health Organisation criteria, 94% of students were classified as anaemic. Preliminary results indicated that 6.8% of students had a haemoglobin level less than 100 g/L, 85% between 100–145 g/L, and 8.1% greater than 145 g/L. The mean haemoglobin level was 124.8 g/L (CI 123.0–126.6) which was significantly lower from 2016 when it was 133.2 g/L (CI 131.8–134.7). Initial results show no significant differences based on age or sex.

Conclusions Data continues to reinforce that there is an extremely high burden of anaemia in this population. Previously implemented strategies do not seem to be having a significant effect in lowering the rates of anaemia. Novel strategies such as increased government food subsidies, alternative iron-rich foods, or sustainable dietary iron supplementation need to be advocated for, developed, and implemented.

312 INCORPORATION OF MULTIPLE COULOMB SCATTERING IN THE PREDICTION OF OPTIMAL FOCAL LENGTHS IN MAGNETICALLY FOCUSED PROTON RADIOSURGERY

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Purpose of study Magnetic focusing of protons is a promising approach to improve patient radiation dose distribution in proton radiosurgery. The paths of individual protons are

affected by multiple atomic deflections (multiple Coulomb scattering (MCS)) and affect overall beam characteristics in the patient. The purpose of this project is to account for the effects of MCS in the optimisation of focal lengths in magnetically focused proton radiosurgery.

Methods used Monte Carlo (MC) computer simulations were performed on magnetically focused proton beams wherein phase space data (i.e., individual particle angle and displacement from beam axis) were collected at the upstream surface of a water tank and at Bragg depth. Phase space data at Bragg depth was also calculated using a second method that incorporated a statistical model of MCS. The change in particle angle and displacement due to MCS was determined in multiple steps along the beam path from the water tank to Bragg depth using a Gaussian approximation and an inverse transform sampling method. Second order statistical moments of angle and displacement were then calculated to generate the so-called sigma matrix, which characterises essential properties of the phase space data. The sigma matrix calculated at Bragg depth using the MCS model was compared to the sigma matrix determined from the MC simulations.

Summary of results Preliminary results suggest that a simple Gaussian approximation of angle and displacement can reproduce the elements of the sigma matrix within an error of 15% compared to the original MC simulation. The model and analysis of MCS are continuously being revised; the latest results will be presented.

Conclusions Optimisation of magnetic focal lengths is important for future individualised radiosurgery treatment plans. Previous efforts in our lab to predict optimal focal lengths included the properties of focusing magnets but not the effects of MCS. The present research represents an ongoing effort to effectively model MCS and incorporate its effects in the prediction of the optimal focal lengths of a magnet focusing system.

313 CMV INDUCED HEMOPHAGOCYTIC SYNDROME IN A CHILD WITH ACUTE LEUKAEMIA

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Conclusions Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome of multisystem inflammatory response with poor outcome if not diagnosed and treated early. Although Cytomegalovirus (CMV) disease is rare in non-transplant children with acute lymphoblastic leukaemia (ALL), it can lead to HLH in the setting of immunosuppression. We hereby describe a paediatric ALL patient, presenting with prolonged fever and pancytopenia who was found to have HLH triggered by acute CMV infection. A three-year-old girl with high risk precursor B-ALL was admitted with febrile neutropenia during maintenance therapy. She had fever for two days without any other associated symptoms. Her physical exam was unremarkable other than petechiae and hepatosplenomegaly. The complete blood count on admission showed pancytopenia. Cefepime was started empirically after blood cultures were drawn. The bone marrow biopsy was done as the fever persisted which revealed occasional hemophagocytosis without

any blasts. She was diagnosed with HLH as she fulfilled the 6 of 8 criteria including phagocytosis, fever, splenomegaly, cytopenia, hyperferritinemia of 18,783 ng/mL and hypertriglyceridemia. She was started on prednisone at 1 mg/kg/day, which was increased due to recurrence of fever with increased ferritin levels. Soluble IL-2 receptor was also above diagnostic levels. Microbiologic tests for the underlying cause of HLH revealed >2 million IU/mL of CMV PCR. Ganciclovir was started and two days later fever resolved. Eye exam was negative for retinitis. She was discharged home on oral valganciclovir and completed total four weeks of antiviral therapy. On her last follow-up, three months after discharge, her CMV PCR was undetectable, ferritin levels were downtrending and she continued the maintenance chemotherapy. There are only five cases similar to our patient in the literature that were shown to have CMV-induced HLH in paediatric ALL. All of them were treated with antiviral therapy, while in two cases steroids and in one also intravenous immunoglobulin were given. In conclusion, we suggest that antiviral therapy in addition to HLH treatment should be considered until CMV viremia is undetectable. As CMV-induced HLH is a rare phenomenon in non-transplant ALL patients, genetic testing can be performed for a possible predisposition.

314 THE TALE OF LUPUS AND THE LIVER: PYLEPHLEBITIS UNVEILING A CHRONIC DISEASE

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10.1136/jim-2017-000663.314

Background Pylephlebitis, or infective suppurative thrombosis of the portal vein, is a rare complication of abdominal infection. The diagnosis is often missed due to nonspecific clinical findings. The most common presenting symptoms include abdominal pain and fever. It is a serious condition with significant morbidity and mortality.

Case description A 55 year old Caucasian male with past medical history of hypertension, coronary artery disease status post stent placement, diverticulitis, and atrial fibrillation presented to the ER with severe abdominal pain accompanied by nausea and vomiting. Bowel sounds were present, there was no abdominal distention, and Murphy sign was negative. On admission, pertinent labs included: WBC 11.8, Hgb 12.2, Hct 35.6, MCV 94.1, Plt 257, absolute neutrophil count 10,300, Cr 1.43, BUN 24, AlkPhos 112, AST 42, ALT 69.

Ultrasound showed no definite cholelithiasis or ultrasound evidence of cholecystitis. The liver was heterogeneous and possible masses were not excluded. The main portal vein measured 10.6 mm and appeared partially occluded suggestive of thrombus or tumour thrombus with suggestion of collateral flow, including in periportal regions. A CT of the abdomen confirmed a right portal vein thrombus. The liver appeared heterogeneous with a denser right lobe and a 6 cm hypodense lesion at periphery of right hepatic lobe extending to gallbladder region along with other smaller mostly right hepatic hypodensities. Pertinent labs included: a negative Factor V Leiden (R506Q) mutation, positive lupus anticoagulant, protein C activity of 63%, normal flow cytometry for CD 55 and CD 59, negative HIV Ab/Ag screen, negative Hepatitis A/B/C

panel, normal AFP tumour marker of 1.0, normal CA 19–9 of 13, normal CA 125 of 29, and a normal Cea of 3.6. Patient then had a CT guided liver biopsy of the right hepatic lobe mass with path showing liver parenchyma with diffuse moderate micro and macrosteatosis, focal abscess formation with necrosis, PAS stain was negative. Given the positive lupus anticoagulant on work-up, patient was started on subcutaneous Lovenox daily for at least 3 months of therapy for portal vein thrombosis.

315 THE UNMASKING OF TWO UNKNOWN; INCIDENTAL HIV DERIVED FROM A UNIQUE LYMPHOMA

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Introduction Plasmablastic Lymphoma (PBL) is a non-Hodgkin's lymphoma that predominantly occurs in the head, neck and oral mucosal region of immunocompromised HIV patients. The prevalence of oral cavity PBL is 1.66% in immunocompetent patients and 7.3% in HIV positive patients. We present a case of a 33 year old male with unknown diagnosis of HIV who presented with a painful right mandibular mass. Histopathological examination revealed large, atypical lymphoid cells with plasmablastic appearance, positive for Epstein Barr virus.

Case This is a 33-year-old previously healthy male who presented to our hospital with 6 months of lower right mandibular pain and swelling. Prior to this admission, patient was seen by his dentist and was given oral antibiotics for possible dental abscess. He also had a right molar extraction when the symptoms were not resolved with antibiotics. Persistence of symptoms after antibiotic therapy and tooth extraction then prompted a visit to the emergency department. On physical examination, a soft tissue mass at the site of the tooth extraction extending along the posterior oral mucosa was noticed. He was referred to oral surgery, and biopsy of the mass confirmed the diagnosis of Plasmablastic Lymphoma with a subsequent positive HIV test. Patient received intrathecal Methotrexate chemotherapy and 5 cycles of V-EPOCH therapy. Intrathecal Methotrexate was administered due to high risk of CNS metastasis in PBL. Since finishing this extensive chemotherapy, patient currently remains in remission and is PBL free. He is currently on HAART therapy with no further complications of his HIV.

Discussion HIV patients have an increased risk of developing non-Hodgkin Plasmablastic lymphoma that have a tendency to occur in the oral cavity as a dental mucosal mass. V-EPOCH therapy along with surgery, radiation or a combination of the three has shown to decrease mortality and prolong survival in HIV-associated PBL patients with complete remission and rare recurrence of the disease.

In an immunosuppressed patient, it is crucial to perform an extensive oral cavity physical examination to rule out HIV-associated-manifestations.

Infectious diseases II

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

316 ANALYSIS OF THE EUKARYAL MICROBIOME OF THE LUNG BY 18S RIBOSOMAL RNA IN CYSTIC FIBROSIS PATIENTS

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Purpose of study Cystic fibrosis (CF) is the most frequently inherited autosomal recessive life-shortening disease in people of European descent. Recurrent lung infections and the consequent inflammatory response in the lungs result in airways damage, the leading cause of morbidity and mortality in these individuals. The bacterial microbiota of the lungs in CF have been extensively characterised by culture as well as by culture independent methodologies. In contrast, much less is known about the fungi associated with CF, which have been characterised primarily by culture-based techniques. We expect that analysing the fungal microbiome of the lung by amplification of 18S ribosomal RNA will reveal a more diverse fungal microbiome than indicated by culture.

Methods used Bronchoalveolar lavage samples were collected from paediatric CF patients as well as disease control patients from 13 different institutions in the United States. DNA was extracted from the resultant lavage fluid. The fungal DNA from 90 patient samples was amplified using barcoded, broad-range 18S rRNA PCR primers. The pooled amplicons were sequenced on an Illumina MiSeq platform. Samples that produced less than 5000 sequence reads were removed from the analysis.

Summary of results Sixty-seven eukaryal taxa were detected by sequencing, with a median of 24 035 sequence reads per sample. Sixty-six out of 89 patient samples were positive for fungal DNA by 18S rRNA PCR. Of these 66 samples, 30 (45%) of these samples were culture negative. Of the samples that were positive by both methods, an average of 5 fungal taxa per sample was detected by 18S PCR while an average of 1.3 fungal taxa per sample was detected by fungal culture.

Conclusions The fungal microbiome of the lung in cystic fibrosis patients is more diverse by 18S rRNA PCR than previously indicated by fungal culture. Our data suggests that fungal species are present in the lungs of most of these patients, yet they often go undetected by culture.

317 RISK FACTORS AND CLINICAL OUTCOMES DUE TO RESPIRATORY SYNCYTIAL VIRUS HOSPITALISATION IN ADULTS

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10.1136/jim-2017-000663.317

Purpose of study Respiratory syncytial virus (RSV) is increasingly recognised as a significant pathogen in adult populations, with a disease burden comparable to influenza. We sought to compare clinical characteristics of adults with RSV and influenza in an indigent, inner city hospital to identify a target population for potential vaccination.

Methods used Electronic chart review was performed for adults ≥ 18 years of age with RSV or influenza A/B detected by PCR admitted to Harborview Medical Centre in Seattle, WA between July 2016 and June 2017. Sepsis criteria was defined by 2 or more of the following: WBC $>12,000$ cells/mm³ or <4000 cells/mm³, heart rate >90 beats/min, respiratory rate >20 breaths/min, and temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$.

Summary of results RSV was detected in 72 of inpatients as compared to 283 with influenza. Patients hospitalised with RSV were more likely to be homeless (29/72 (40%) vs 76/283 (30%); $p=0.026$) compared to those with influenza. Patients admitted with RSV were also more likely to meet sepsis criteria (42/84 (50%) vs 107/290 (14.5%); $p=0.03$), have longer hospital duration (4.96 (SD: 7.96) vs 3.34 (SD: 7.21); $p=0.008$), be admitted to the ICU (18/84 (21%) vs 37/290 (12.8%); $p=0.0039$), and to be readmitted due to RSV or influenza (20/72 (28%) and 6/283 (2%); $p=0.00001$).

Conclusions RSV represents a significant burden of viral pneumonia in an indigent, inner-city population in the U.S. with unique risk factors and increased disease severity as compared to influenza. Introduction of vaccination has the potential to significantly reduce health care utilisation in this high-risk population.

318 YYCF E207K: A PROBE TO STUDY ANTIMICROBIAL AGENTS THAT TARGET THE ESSENTIAL YYC G KINASE

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10.1136/jim-2017-000663.318

Purpose of study Antimicrobial drugs that exploit novel targets and overcome existing antimicrobial resistance mechanisms are desperately needed. Bacterial two component systems (TCS) have garnered interest as targets due to their involvement in essential processes and their absence from mammalian genomes. We recently identified a series of thiophene derivatives that showed promising antimicrobial activities and inhibited the YycG kinase of the essential YycFG TCS of *Bacillus subtilis*, a close relative of several important human pathogens. A constitutive YycF transcription factor mutant capable of functioning in the absence of the YycG kinase would be highly valuable in evaluating these and other drugs, and assure that kinase inhibition is the reason for their antimicrobial effect. We describe the isolation and characterisation of such a mutant, YycF E207K.

Methods used We engineered a strain that allowed for induced excision of the native *yycFG* locus. Upon excision, growth of *B. subtilis* solely relies on the presence of an engineered ectopic *yycF* E207K copy. Western-Blot analysis was performed to compare E207K to wild type *yycF* expression. To assure constitutive YycF transcription factor activity, the expression of the *cwlO* autolysin gene was tested by RT-PCR.

Summary of results YycF E207K indeed supports growth of *B. subtilis* in the absence of YycG kinase. YycF protein levels are unchanged between wild type and mutant. Yet, *cwlO*

expression is constitutively causing cells to lyse after prolonged incubation. This phenotype induces the accumulation of secondary mutations to generate stable isolates. We are currently utilising this strain to determine minimal inhibitory concentration (MIC) of compounds that target YycG kinase.

Conclusions Data from our bacterial growth studies of YycF E207K proved that *B. subtilis* can grow in the absence of YycG kinase due to constitutive activation of autolysins. We now have the means to evaluate the specificity of histidine kinase inhibitors. We expect *B. subtilis* carrying the mutant *yycF* E207K allele to survive in the presence of compounds that target YycG kinase. Application of YycF E207K goes beyond determining the target of our thiophene derivatives, and serves as a tool to screen for novel antibiotics that target YycFG.

319 RISK FACTORS FOR INDETERMINATE OUTCOME ON INTERFERON GAMMA RELEASE ASSAY FOR LATENT TUBERCULOSIS IN UNITED STATES IMMIGRANTS

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Purpose of study Early detection and treatment of latent tuberculosis infection (LTBI) greatly reduces the likelihood of progression to active TB. Foreign-born patients account for most of the TB in the US. Interferon gamma release assay (IGRA) is the preferred diagnostic test for LTBI, but it has not been studied extensively in immigrants and can sometimes produce an indeterminate result. We investigated the prevalence of and risk factors for an indeterminate IGRA (IND-IGRA) in a diverse cohort of US immigrants.

Methods used We identified patients ≥ 18 years old who had an outpatient IGRA between 2010–2017 in our health system and restricted to those whose primary language was non-English, as a surrogate for immigrant status. For patients with >1 IGRA, we analysed the first outpatient IGRA. We examined the following covariates, using univariate and multivariate logistic regression, for association with the outcome IND-IGRA: sex, age, race, diabetes, chronic kidney disease, anaemia, hypoalbuminemia, and liver disease (by AST-platelet ratio index).

Summary of results A total of 3131 patients had at least 1 outpatient IGRA done, of whom 121 had an initial IND-IGRA for a prevalence of 3.9%, 95% CI: 3.2% to 4.6%. Our cohort was 32% Asian/Pacific Islander (PI), 30% Hispanic, and 28% black; 44% were men and the median age was 50. In multivariable analysis, Asian/PI race (referent: Hispanic, adjusted odds ratio [aOR] 3.0, 95% CI: 1.8 to 5.0) was independently associated with IND-IGRA. Anaemia, hypoalbuminemia and liver disease were each associated with IND-IGRA in univariate analysis but no longer significant when adjusted for other factors. There was however significant effect modification between anaemia and hypoalbuminemia (aOR for interaction 3.9, 95% CI: 1.2 to 12.9). Those with anaemia and hypoalbuminemia accounted for 33% of IND-IGRAs and their rate of IND-IGRA was 19%.

Conclusions Asian/PI race and the interaction of anaemia/hypoalbuminemia were independent risk factors for an indeterminate IGRA outcome. The latter combination may be surrogate for impaired immunologic response mediated by inflammation

or other comorbid conditions. Our findings suggest IGRA may not be the optimal modality for detecting LTBI in patients with anaemia and hypoalbuminemia.

320 RISK OF NEUTROPENIA WITH LONG TERM ANTIMICROBIAL THERAPY IN PAEDIATRIC PATIENTS WITH OSTEOARTICULAR INFECTIONS

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Purpose of study Osteoarticular infections are a common indication for prolonged antimicrobial therapy in children. Little is known about the characteristics of antimicrobial-induced neutropenia despite the frequency with which it occurs.

Methods used Patients (1 month-18 years of age) admitted to the University of New Mexico between 2004–2015 were identified by 40 different ICD-9 discharge codes for osteoarticular infections. Each chart was reviewed, and patients with verified septic arthritis or osteomyelitis were included. Excluded patients included those with no baseline absolute neutrophil count (ANC) prior to the first antibiotic dose, incomplete dosing information, infected orthopaedic implants, neonates, immunocompromised patients or those with a post-operative infection. Data collected included demographic information, ANC values, antibiotic choice and duration of therapy. Neutropenia was defined as an ANC below 1500 and decreasing.

Summary of results 186 subjects were included (67.2% male), with ages ranging from 0.3 to 17.9 years (mean 7.6 years). Patients presented with osteomyelitis (58.4%), septic arthritis (26.5%) or both (15.1%). Of the 186 subjects, 61 (32.8%) developed neutropenia while on antimicrobial therapy. A total of 1,304 ANC values were obtained, ranging from 0 to 14,442 cells/mcL (mean 5,067 cells/mcL). Of those, 118 values met criteria for neutropenia, ranging from 0 to 1,496 cells/mcL (mean 1,048 cells/mcL). The time to the first neutropenic episode ranged from 2 to 340 days (median 24 days). Neutropenic patients were more likely to have received a beta-lactam as part of their treatment regimen than non-neutropenic patients (96.7% vs 92.0%, $p=0.0803$). Neutropenic subjects were more likely to have received courses of therapy greater than 8 weeks duration (41.0% vs 27.4%, $p=0.0369$). Of those with neutropenia, only one subject required GCSF, while 20 exhibited spontaneous recovery of their ANC. The lowest ANC value with spontaneous recovery was 702 cells/mcL. No patients suffered any complications from their neutropenia.

Conclusions Neutropenia, though common during treatment of osteoarticular infections in children, appears to be well-tolerated and frequently spontaneously resolves.

321 EFFECT OF PLASMA ON IN-VITRO BLOOD BRAIN BARRIER

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Purpose of study Children living with HIV are vertically infected within the first two years of life during which they can develop neurocognitive impairment. Understanding the dynamics of HIV transmission across the blood brain barrier (BBB) has implications for paediatric neuroAIDS as knowledge of neuropathogenic processes are needed. Plasma from HIV-seropositive individuals comprise of different cytokines that may cause BBB disruption and ultimately NCI. The study aimed to determine the effects of plasma on a BBB model for future clinical research studies. The hypothesis is to identify a specific plasma concentration on the BBB model which would be optimal for BBB studies using clinical specimens.

Methods used The *in-vitro* BBB model was established by co-culturing endothelial cells and astrocytes on a 0.3 µm insert. Control fresh and frozen HIV-seronegative plasma from one individual was titrated from 0%–25% and placed on an insert. Four inserts were used per plasma concentration for a total of 48 barriers. The barriers were assessed using TEER (transendothelial electrical resistance) and EBA (Evan's blue dye in bovine serum albumin) to characterise the blood brain barrier integrity.

Summary of results Increased plasma concentration resulted in greater BBB disruption noted by decreased TEER values and increased EBA values for fresh and frozen plasma but with a lower effect using frozen plasma.

Conclusions The study demonstrated that 5% frozen plasma was an optimal concentration with minimal barrier disruption. The importance of the concordance findings is ideal since patient plasma can be stored until BBB experiments are ready to be performed. Future studies plan to investigate the effects of HIV-seropositive plasma on the BBB with applications for paediatric neuroAIDS clinical studies. Determining the effect of blood plasma on the BBB can help gain a greater understanding of plasma contributions to BBB disruption and ultimately link the effects of plasma to NCI. (Partially funded by Whitman Internship Grant, NIH Grant R01MH10219).

322 COSTING EVALUATION OF TUBERCULOSIS RULE OUT TESTS TO IMPROVE ISONIAZID PREVENTATIVE THERAPY UPTAKE IN PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS

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Abstract 321 Figure 1 The graph on the left represents TEER results that reveal decreased resistance as plasma concentration increased. On the right, EBA results reveal increased percent permeability as plasma concentration increased. Both decreased TEER and increased EBA results represent disruption of BBB integrity. Note the elevated effect of fresh plasma on EBA results

Purpose of study The objective is to determine the incremental annual costs of alternative methods of tuberculosis screening in HIV + individuals compared to the current World Health Organisation (WHO) recommended symptom screen and GeneXpert in Ahero and Kisumu County, Kenya.

Methods used To estimate the real world delivery costs (in USD, in 2017) of various tuberculosis screening methods, we conducted a micro-costing and time and motion analysis within a prospective interventional study of tuberculosis screening pre- and post-completion of isoniazid preventative therapy in Nyanza, Kenya. Specifically the costs for sputum collection, liquid culture, fluorescence microscopy, GeneXpert, tuberculin skin test (TST), and blood draws for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Using Ministry of Health costs and interviews, the implementation costs of the tuberculosis screening methods were estimated for a government hospital.

Summary of results In June 2017, costing was conducted in US dollars. Average times per patient per screening method estimated for implementation in Comprehensive Care Centres (CCC) from the time and motion study are as follows: collecting patient sputum samples took 8–10 min, blood draw and collection for C-reactive protein and erythrocyte sedimentation rate took 6–8 min, TST administration and follow up took 13–15 min. With the hiring of one additional nurse, each hospital CCC site for three mornings a week could see 2400–2769 patients for tuberculin skin tests and follow-up, 4500–6000 patients for blood collection for ESR and CRP testing, and 3600–4500 patients for sputum collection in one year. A four-cartridge GeneXpert machine can process a maximum of 4000 samples in one year. The clinic and lab costs per patient are as follows: TST \$1.72 USD, blood draw for ESR and CRP \$4.70 USD, GeneXpert \$12.20 USD, fluorescence microscopy \$4.30 USD, and liquid culture \$4.30 USD. Using these costing results, various TB screening algorithms were explored.

Conclusions Alternative TB screening algorithms have the potential to detect active TB earlier in HIV patients, a high risk population, at lower cost than the WHO recommended GeneXpert. These costing estimates can inform mathematical models evaluating the cost-effectiveness of TB screening algorithms.

323 DIAGNOSIS OF PNEUMOCYSTIS PNEUMONIA – A RETROSPECTIVE STUDY 2014–2017 OF PATIENTS PRESENTING AT AGA KHAN HOSPITAL, NAIROBI, KENYA

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Purpose of study *Pneumocystis jirovecii* pneumonia (PCP) is an opportunistic fungal infection that occurs in immunocompromised individuals. PCP is difficult to diagnose due to the non-specific clinical symptoms and the simultaneous multiple infections common in immunocompromised patients. In an effort to come up with diagnostic criteria for PCP, our retrospective study reviews the medical charts of patients suspected of PCP that have undergone bronchial alveolar lavage (BAL).

Methods used This study was conducted at Aga Khan University Hospital (AKUH) in Nairobi, Kenya. We retrospectively

reviewed the medical charts of all the patients that had BAL procedure during the study period, September 2014 through March 2017. The following data were recorded for analysis: age, sex, lab findings, microscopy examination, PCP PCR results, chest imaging findings and evolution (X-ray/CT scan when available), clinical signs at the time of diagnosis, HIV/AIDS status, immune background, haemodynamic status, response to therapy including anti-pneumocystis, and antibacterial agents and presence of other comorbidities.

Summary of results A total of 266 BAL samples were received from patients with suspected PCP during the study period; 85 HIV positive, 94 HIV negative and 87 unknown HIV status. Of the 85 known to be HIV positive, 24 samples were found to be PCP positive with PCR compared to 8 of the non-HIV patients. The samples that were found to be PCP positive (7 cases) with microscopy examination were all from HIV positive patients. The mean cycle threshold (Ct) of PCR is significantly lower in the HIV-infected patients with positive cytologies (19.1) than the 16 with negative cytologies (27.0) who had a recorded Ct value. Thus, on the average, there was a greater than two-log greater number of organisms in the patients with positive cytologies.

Conclusions PCR is more sensitive than cytology, but because of colonisation without disease that can be identified by PCR, the clinical specificity must be determined in order to know the exact role of PCR in the diagnosis of Pneumocystis disease.

324 COCCIDIOIDOMYCOSIS MENINGITIS WITH HYDROCEPHALUS AND SHUNT REVISIONS

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Purpose of study The purpose of this study to describe the epidemiologic and co-morbidities in patients with coccidioid meningitis with hydrocephalus who have ventriculo-peritoneal (VP) shunt requiring shunt revisions.

Methods used Data Collection –In this retrospective study, 56 patients were identified with inclusion criteria of having coccidioid meningitis with hydrocephalus requiring a ventriculo-peritoneal (VP) shunt. Data was collected through uniform query of community hospital database from the years 2007–2017. Data was collected on patient demographics, medical history, social history, number of revisions and the time between each revision.

Summary of results Of the 56 patients who had coccidioid meningitis with hydrocephalus requiring VP shunt placement, 64% (36/56) had at least one revision. Of the subset that needed at least one VP shunt revision, 56% (20/36) were Hispanics. Of the 56 patients who required VP shunt placement 64% (36/56) were males. The average age of patients requiring at least one shunt revision was 44. BMI of requiring at least one shunt revision was 27.6. Of the 36 patients who required at least 1 revision, only 4 had diabetes mellitus, and if haemoglobin A1C was 9 or greater, they required at least 2 revisions. Of the patients requiring at least 1 revision, 14 had hypertension, 7 had dyslipidemia, 1 had HIV, none had pulmonary tuberculosis and 9 had tobacco dependence. Of the patients who had at least 1 revision, 16 had a revision within first 12 months while 5 had a revision within 24 months. Of

the patients who had a shunt complication within the first 12 months, they were more likely to have additional revisions.

Conclusions More than one half of patients with coccidioid meningitis with hydrocephalus who had VP shunt placement required at least one revision. The placement of a shunt can lead to infection or failure of the shunt requiring a revision in 72% of our patients. If the patient is a Hispanic male, there is increased likelihood of a VP shunt revision based on our data collection. Further studies are warranted to determine the impact of shunt placement and other variables associated with complications.

Morphogenesis and malformations

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

325 DELINEATION OF THE CLINICAL AND BEHAVIOURAL PHENOTYPE IN CHILDREN WITH *PPM1D* VARIANTS: SIMILARITIES TO WILLIAMS SYNDROME?

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Case Report Fourteen individuals with heterozygous *de novo* germline truncating variants in *PPM1D* were recently described by Jansen et al. (AJHG 100:650–58. 2017) as a new cause of intellectual disability with frequent poor growth, hypotonia, feeding problems, behavioural abnormalities, and episodic vomiting. Several children had hyperacusis, and anxiety.

We report the clinical phenotype in two new cases and expand on two previously reported cases.

Case 1 was seen first at 17 months for developmental delay, hypotonia, short stature, feeding problems, and poor growth. Studies including SNP array and MRI were normal though small optic nerves were noted and he was placed on growth hormone. He was re-referred at age 3 because of features of Williams syndrome including hyperacusis, extreme sociability, high pain threshold, anxiety, no sense of danger, tantrums and echolalia. Trio exome sequencing was interpreted as normal but results were reinterpreted in 2017 and a truncating *de novo* frameshift variant in *PPM1D* reported (c.1269_1270delGG).

Case 2 presented at age 3 to rule out Williams syndrome. He had significant delay but no neonatal problems or medical issues. SNP array was normal but mother/child exome sequencing revealed a heterozygous truncating variant in *PPM1D*. Both children have some craniofacial findings seen in Williams syndrome including supraorbital fullness, wide mouth, and widely spaced teeth. They lack other cardinal features but have a striking Williams-like personality.

Case 3, previously reported, has hyperacusis, sensory and attention issues. He has a *de novo* variant in *PMM1D* [c.1210C>T (p.Gln404*)]. Case 4, previously reported, now

11 years old, has an IQ of 96, but difficulty with math and reading, anxiety, ADHD and episodic vomiting. Trio sequencing revealed [c.1339G>T (p.Glu447*)].

PPM1D is a cell cycle checkpoint gene expressed in the fetal and adult brain. *Pp1md* deficient mice show an increase in anxiety and depression-like behaviour suggesting a role for *PPM1D* in mood stabilisation. Standardised tests are planned to further analyse these four children's behavioural phenotype, the propensity to vomit and their resemblance to Williams syndrome.

326 PHACOMATOSIS PIGMENTOVASCULARIS: A CASE WITH SOMATIC MUTATION IN *GNAQ* AND ATYPICAL PHENOTYPIC FEATURES

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10.1136/jim-2017-000663.326

Case Report Phacomatosis Pigmentovascularis (PPV) comprises a family of rare disorders that feature vascular and pigmentary nevi that can be cutaneous or multisystem in nature. *Happle et al.* proposed three subtypes of PPV based on cutaneous findings: cesioinflammia, spilorosea, and cesiomarmorata. Recent work by *Thomas et al.* demonstrated that vascular findings and pigmentary nevi in PPV can result from somatic mosaic activating mutations in the genes *GNAQ* and *GNA11*. Recurrent mutations in *GNAQ* have been seen in uveal melanoma, congenital hemangioma, and the multisystem disorder Sturge-Weber Syndrome. Here we present the case of an 11-year old boy with phacomatosis cesioinflammia with mutation in *GNAQ* and review the literature on this condition.

At birth, the child was diagnosed with a capillary malformation of the right face, neck, shoulder and arm as well as hyperpigmentation of the clear part of the right eye, right central palate and right ear and left upper arm. He had gradual overgrowth of the right leg and prominent superficial collateral veins on his back and thighs with MR imaging showing absence of multiple deep veins. His cognitive development and growth is typical for age although he recently has developed subtle myoclonus with normal brain MRI. He has no family history of these skin changes.

We performed whole exome sequencing of his blood as well as of affected skin. No *de novo* events were detected in his blood. Sequencing of his skin biopsy found a mosaic *GNAQ* mutation c.548G>A, p.R183Q in 12 of 211 reads which was confirmed by Sanger sequencing. Our case expands the phenotype of phacomatosis cesioinflammia with a mutation in *GNAQ*. Myoclonus has not been identified as a feature of this disorder and may represent a novel manifestation. Our findings also provide additional molecular evidence to the hypothesis from *Thomas et al.* that PPV results from somatic activating mutations in *GNAQ* and *GNA11* and suggests that PPV lies on a continuous phenotypic spectrum of diseases involving pigmentation and vasculature from isolated congenital hemangioma to Sturge-Weber Syndrome.

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DIAS-LOGAN SYNDROME: DELINEATING A NEWLY RECOGNISED DISORDER OF TRANSCRIPTIONAL REGULATION

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Purpose of study Dias-Logan syndrome is a recently described condition characterised by intellectual disability (ID) and persistence of fetal haemoglobin (HbF). It is caused by haploinsufficiency of *BCL11A*, on 2 p16.1, encoding a transcription factor belonging to the SWI/SNF chromatin remodelling complex. We describe 3 newly diagnosed patients, and discuss additional clinical features and pathogenesis.

Methods used We reviewed the medical records of our patients with changes in *BCL11A* and those in the literature, and assessed the frequency of the main manifestations.

Summary of results Our patients, aged 8–11 y, presented with hypotonia (3/3), ID (3/3), persistence of HbF (3/3), brain abnormalities (3/3), strabismus (2/3), and seizures (2/3). Two of them had *de novo* deletions involving *BCL11A*, and one had a *de novo* pathogenic variant in *BCL11A*.

By review of the literature, we found 13 additional individuals with point mutations and 25 with 2 p15p16.1 microdeletions, aged 21 m–32 y. Including our patients, the most frequent manifestations were ID (100%), varying from mild to profound, persistent HbF (100%), distinctive facial features (95%), hypotonia (84%), microcephaly (63%), abnormal brain MRI (71%), consisting of cortical dysplasia, corpus callosum hypoplasia, or cerebellar hypoplasia, and growth delay (42%). Epilepsy was present in 15%: age at onset ranged 2 m–3 y, and seizures were drug-resistant in most cases. Interestingly, in half of the patients the facial gestalt resembled Alfa Thalassemia Intellectual Disability (ATRX), a condition caused by mutations in a gene encoding another SWI/SNF-like protein.

Conclusions Our study expands the phenotype of *BCL11A* mutations to include early onset seizures and brain abnormalities, and the overlapping manifestations between Dias-Logan syndrome and ATRX syndrome suggest convergence on a common pathway of transcription regulation of haemoglobin genes.

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MESENCHYMAL LOSS OF VEGFR2 LEADS TO ABNORMAL LUNG MORPHOLOGY

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Purpose of study Inflammation and infection inhibits normal lung development in preterm infants. Based on human and animal studies, inflammatory mediators that activate NF- κ B disrupt expression of genes required for normal development. Our lab previously showed that the TLR4/NF- κ B activator lipopolysaccharide (LPS) altered fetal mouse lung mesenchymal cell morphology and inhibited the expression of specific developmental genes, including the VEGF receptor *Vegfr2*. Although VEGF signalling is known to regulate lung vascular development, the potential role of *Vegfr2* in the mesenchyme is not known. In this study, we used a targeted deletion strategy to

determine the role of mesenchymal *Vegfr2* in mouse lung development.

Methods used Mice expressing a loxP flanked *Vegfr2* allele were crossed with the mesenchyme specific *Twist2Cre* transgenic strain. The resulting *Twist2 Δ Vegfr2* mutant mice were confirmed by PCR based genotyping. Changes in lung structure and cell morphology were assessed by Hematoxylin and Eosin staining of adult lung tissue. Elastic fibres were visualised using a modified Hart's stain. Epithelial cell height was measured using image analysis of multiple mice of each genotype. *Twist2 Δ Vegfr2* mice were compared to control littermates for each set of experiments by Student's *t*-test or ANOVA.

Summary of results Mutant *Twist2 Δ Vegfr2* were present in expected Mendelian ratios suggesting embryonic and perinatal viability. As the mice developed, *Twist2 Δ Vegfr2* mice were smaller than their control littermates with reduced weight. In adult *Twist2 Δ Vegfr2* mice, we noticed abnormal epithelial morphology in the conducting airways of *Twist2 Δ Vegfr2* lungs, with flattened, dysplastic epithelial morphology. Image analysis measured reduced height in the bronchi of *Twist2 Δ Vegfr2* mice (0.012 ± 0.08 mm in *Twist2 Δ Vegfr2* mice, 0.034 ± 0.04 mm in littermate controls; $p < 0.01$, $n = 3$). *Twist2 Δ Vegfr2* mice had reduced elastic fibre staining throughout the alveolar region.

Conclusions Our data suggest that a *Vegfr2* is required in the lung mesenchyme for normal epithelial and alveolar development. These findings suggest an important crosstalk mechanism between lung mesenchyme and adjacent epithelial cells that could be disrupted by inflammation and loss of *Vegfr2* expression.

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PERINATAL DISTRESS IN 1P36 DELETION SYNDROME

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Purpose of study In a large case series of individuals with 1 p36 deletion, Battaglia et al. (2008) reported that 'birth history was notable in 50% of the cases for varying degrees of perinatal distress'. Specifics were not given. There have been children reported with periventricular leukomalacia which can be a finding attributed to HIE. The purpose of this study was to examine a case series of individuals with 1 p36 deletion specifically for evidence of perinatal issues.

Methods used Chart review of all cases of 1 p36 deletion identified through our cytogenetics lab since 1990 was performed. Information reviewed included: gestational age, mode of delivery, Apgar scores, mode of resuscitation (if needed), brain abnormalities on imaging, age at discharge and evidence of seizure disorder.

Summary of results Of the 13 cases of 1 p36 deletion identified, 10 had sufficient information to be included in this review. Eight were term and one gestational age was not identified. Of the 5 patients for whom Apgar scores were noted, the average 1 min score was 3.8. Resuscitation for these children varied and included warming and stimulation, intermittent PPV, CPAP, intubation, and chest compressions. Of the 9 children who had brain imaging, 6 had abnormalities which included white matter abnormalities, cysts, periventricular leukomalacia and increased fluid. Five children were discharged home with their mother while others remained inpatient from 6 days–1 month. Five of these children had seizure disorder diagnosed by 8 weeks of age.

Conclusions Based on our case series, most children were born at term and therefore one would suspect not needing vigorous resuscitation. However, the average 1 min Apgar score was low and various forms of resuscitation were required in the majority. As cited in Gene Reviews, 44%–58% of children with 1 p36 deletion syndrome have seizures and indeed, half of our patients examined also had seizure disorder. Based on our findings, we postulate that children with 1 p36 deletion syndrome have perinatal findings of distress that may be attributable to their deletion syndrome. We further question if some cases could be misdiagnosed as HIE. We plan to extend this study to include cases from other institutions to determine whether perinatal issues are indeed part of the 1 p36 deletion syndrome.

330 RECURRENT CASE OF MACROSTOMIA AND CORTICAL DYSPLASIA

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Case Report Macrostomia, in which the mouth measures wide from corner to corner, classically involves failure of fusion of the mandible and maxillary process. This rare anomaly, associated with a dysplastic appearance of the corners of the mouth and underlying bony defects, is seen consistently in the TWIST2-related conditions ablepharon macrostomia syndrome and Barber Say syndrome but can also be seen in isolation.

We present a patient with bilateral macrostomia and cortical brain anomalies similar to a previously reported case. The two patients share a unique combination of major anomalies and a similar facial appearance, suggesting their anomalies share an underlying cause.

Our patient was born following a full-term pregnancy complicated by vanishing twin between 6 and 8 weeks' gestation. He was noted at birth to have macrostomia and presented to Genetics clinic at two months of age. We noted bilateral macrostomia, relative hypertelorism and downslanting palpebral fissures, and overfolded helices; the exam was otherwise normal. Ophthalmology evaluation suggested cortical vision impairment, and an MRI showed extensive bilateral subependymal grey matter heterotopia along the lateral ventricles as well as dysplastic corpus callosum and cortical dysplasia most severe in the right posterior cerebral hemisphere. Chromosomal microarray demonstrated a normal male chromosomal complement. Review of the literature yielded a 2007 report of a male with similar findings: bilateral macrostomia; bilateral subependymal heterotopia; and ventriculomegaly with apparent aqueductal stenosis. The reported patient had a similar facial appearance to our patient.

These two boys present a similar combination of rare anomalies. Though other individuals with macrostomia have rarely been reported to have brain anomalies, those individuals had additional external anomalies. A relationship to twinning can be speculated on, but this entity may represent a unique syndrome or a phenotypic expansion of a known syndrome. TWIST2 is a candidate gene, and exome sequencing should be done to assess this gene and to look for other causes of this phenotype.

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RENAL HYPODYSPLASIA AS A NOVEL FINDING IN THE SIX2 DELETION SYNDROME: CASE REPORT AND REVIEW OF THE LITERATURE

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Purpose of study Our objective is to describe a novel clinical phenotype associated with a *SIX2* whole gene deletion. The *SIX* family of genes plays an important role in early organogenesis. Several genes in this family, including *SIX2*, are expressed during early renal development. *SIX2* is additionally expressed in the first and second branchial arches as well as myogenic sites in craniofacial musculature. Deletion of *SIX2* has previously been linked to frontonasal dysplasia with ptosis and hearing loss.

Methods used Review of case records and literature review were used.

Summary of results Deletions of *SIX2* have been reported in patients with frontonasal dysplasia, ptosis, wide fontanelles, and hearing loss. Haploinsufficiency of *SIX2* in species including mice and zebrafish has been linked to severely dysplastic kidneys. However, evidence for involvement in human renal malformations has been limited. The findings in this case suggest that haploinsufficiency of *SIX2* may result in renal anomalies in humans.

Conclusions Evidence from the present case, genetic studies of human renal hypodysplasia as well as model systems support the conclusion that the phenotypic spectrum of the *SIX2*-related microdeletion syndrome includes variably: typical craniofacial features, hearing loss, and renal anomalies. These findings have implications for genetic counselling and clinical management.

Neonatology general IV

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

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EXPOSURE TO ISOFLURANE INCREASES BILIRUBIN PRODUCTION IN NEWBORN MICE

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10.1136/jim-2017-000663.332

Purpose of study Heme oxygenase (HO) is the rate-limiting enzyme in the bilirubin production pathway. Increased bilirubin production due to hemolysis can lead to severe neonatal hyperbilirubinemia and if left untreated, to bilirubin neurotoxicity. Post-surgical cardiac newborns have been shown to be at an increased risk for developing hyperbilirubinemia and also hemolysis. We have previously found that exposure to isoflurane induces HO-1 expression in adult mice. Therefore, the objective of this study was to evaluate whether isoflurane exposure induces HO-1 and further increases bilirubin production in an acute hemolytic newborn mouse model.

Methods used 3d-old newborn FVB mice pups were exposed to 2% isoflurane for 18 min or air (controls). To first assess HO-1 induction following isoflurane exposure, HO activity in livers were measured 24, 48, and 72 hour post-isoflurane. To evaluate the isoflurane-mediated induction of HO-1 increased bilirubin production, pups were given a heme load (18 mg/kg, s.c.) 24 hour after isoflurane exposure. Pups were then placed in 5 mL chambers supplied with air (~13 mL/min) for measurements of bilirubin production as indexed by total body carbon monoxide (CO) excretion rates (VeCO) and monitored for up to 4 hour. All data were expressed as percent of age-matched control (HO activity) or fold change over baseline (VeCO) levels.

Summary of results Isoflurane significantly increased liver HO activity $120\% \pm 9\%$ and $116\% \pm 17\%$ at 24 hour ($n=8$, $p<0.0001$) and 48 hour ($n=7$, $p=0.01$), respectively, post-exposure. HO activity returned to control levels by 72 hour ($103\% \pm 10\%$, $n=7$). In heme-treated isoflurane-exposed pups ($n=3$), bilirubin production was higher and peaked earlier (3.3 ± 0.3 fold, 2.8 ± 0.5 hour) compared with heme-only-treated pups ($n=3$, 2.7 ± 0.3 fold, 3.3 ± 0.4 hour).

Conclusions We conclude that isoflurane exposure can induce HO-1 expression in the liver, and may explain the development of severe hyperbilirubinemia in post-surgical infants, especially in those undergoing hemolysis.

333 ABO HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN: THIRTEEN YEARS OF DATA AFTER IMPLEMENTING A UNIVERSAL BILIRUBIN SCREENING AND MANAGEMENT PROGRAM

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10.1136/jim-2017-000663.333

Purpose of study ABO hemolytic disease occurs among neonates with blood groups A or B delivered to group O women. Questions remain about the range of severity of this entity. In 2004 Intermountain Healthcare instituted a neonatal bilirubin screening/management program in which all neonates had a total serum bilirubin (TSB) measurement in their birth hospital plotted on a time-specific (Bhutani) chart, and recommendations for management and follow-up were given to the clinician. We sought to determine the odds of developing severe ABO hemolytic disease in the 13 years since adopting this bilirubin screening/management program.

Methods used We conducted a retrospective analysis of neonates born between 2004 and 2016, defining 'severe' hemolytic disease as; 1) TSB >25 mg/dL, 2) hospital readmission for treatment of jaundice, or 3) evidence of acute bilirubin encephalopathy. These three outcomes were tabulated in all neonates born to group O(+) mothers. The control group was composed of neonates not at risk for ABO disease because they were group O, and the study group was made up of neonates at risk for ABO disease because they were group A or B.

Summary of results Of 4 00 531 live births in the 13 year study period, 47% were to group O women; 86% of whom were group O(+). 42 529 (27%) neonates born to group O (+) women had their blood group determined; 29 729 (68%)

were O, 10 682 (25%) A, and 3109 (7%) B. Peak TSBs during the first 10 days were higher in group A (11.0 ± 4.2 mg/dL) and B (11.5 ± 4.3) than group O neonates (10.3 ± 4.1) (A +B vs O $p<0.0001$). However the relative risks of a TSB ≥ 25 mg/dL ($p=0.062$), readmission for jaundice ($p=0.665$), or acute kernicterus were the same in the control vs study groups.

Conclusions In our health system severe hemolytic disease in neonates born to group O(+) woman is not more likely in group A or B neonates than in group O neonates. We recognise that in practices that do not have a bilirubin screening/management program, ABO hemolytic disease severity might be different than in our system.

334 AUTOMATED QUANTIFICATION OF CIRCULATING RED BLOOD CELL FRAGMENTS: CREATING NEONATAL REFERENCE INTERVALS AND USING THESE TO IDENTIFY MICROANGIOPATHIC DISORDERS

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10.1136/jim-2017-000663.334

Purpose of study Schistocytes are circulating fragments of red blood cells (RBC). Their presence indicates intravascular injury of RBC from tethering and tearing as they flow past intravascular fibrin strands. Schistocytes can be identified manually from a blood smear, but automated quantification systems evaluate logs more cells and avoid inconsistencies in human microscopic identification. Reference intervals for schistocytes have not been published for neonates, and the relevance of enumerating schistocytes of neonates by automated methods has not been reported.

Methods used We created reference intervals for schistocytes of neonates using the Fragmented Red Cells (FRC) parameter from Sysmex Haematology analyzers. Data were retrieved from deidentified automated neonatal CBCs from ten Intermountain Healthcare hospitals during the past 28 months. The FRC can be reported as either a percent (% of red cells that are fragmented) or as an absolute number (red cell fragments/ μ L blood). We also sought to discover the clinical conditions of those neonates whose FRC values were very high (exceeding the upper reference interval).

Summary of results New reference charts, based on 39,949 CBCs of neonates, display FRC lower and upper reference intervals on the day of birth according to gestational age, and during the first 90 days after birth. Simultaneous measurements of FRC% and FRC/ μ L had a very high correlation ($R^2=0.895$). Neonates whose FRC exceeded the upper reference interval ($n=96$) clustered into the following groups; 37% had sepsis, 29% had DIC, 17% had trisomy or another genetic syndrome, 14% had necrotizing enterocolitis, 7% had iron deficiency (some had more than one diagnosis).

Conclusions The FRC, as a quantitative measurement of schistocytosis, could be incorporated into each CBC as a useful new NICU laboratory test. Adding it to a CBC takes no more blood volume, run-time, or reagents than needed for a standard CBC. A high FRC indicates significant schistocytosis and could prompt investigation into, or inform follow-up of, a microangiopathic disorder such as DIC.

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PILOT STUDY FOR EARLY IDENTIFICATION OF SHOCK IN NEONATES USING A SCREENING TOOL

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10.1136/jim-2017-000663.335

Purpose of study Shock in neonates causes significant morbidity and mortality. Signs of shock are difficult to differentiate from other physiologic changes in neonates. Screening tools to identify shock and initiate early treatment have demonstrated decreased mortality in adults and paediatric Emergency Departments (ED). Current tools are based on age specific norms and are not routinely used in the Neonatal Intensive Care Unit (NICU). We hypothesise that using a screening tool based on changes from baseline physiologic parameters is feasible, and may improve communication between care providers.

Methods used We created a screening tool from retrospective chart review to identify early signs of shock using the following criteria: temperature instability, heart rate and respiratory changes, hypotension, decreased urine output (UOP), prolonged capillary refill time (CRT), and abnormal complete blood count (CBC). Eight volunteer nurses completed training on use of tool. A prospective study of 22 neonates was conducted from December 1, 2016 – February 28, 2017. A screening tool was applied every 3–4 hours and assessed ease of use in nursing workflow. A positive screen was defined as changes in 2 or more criteria and triggered the nurse to communicate concern for shock with provider.

Summary of results Twenty-two neonates had 127 assessments. Fifteen male and 6 female neonates had a mean gestational age of 31 weeks, and birthweight of 1728 grams. Twenty neonates had all negative screens. Two neonates had all 7 positive screens (5.5%), which triggered communication with provider, but only 2 positive screens (1.5%) required further work-up. Abnormal CBC, decreased UOP, prolonged CRT, and change in respiratory status were the most common triggers. Feedback was positive regarding ease of use (<5 min) and improving communication between care providers.

Conclusions Given the ease of using this tool our next steps include applying the tool on all patients in our NICU and assessing sensitivity and specificity. Other outcome measures will include number of sepsis screens, blood draws for sepsis evaluation, antibiotics<48 hours, positive cultures, and escalation of care. We speculate that early identification and treatment of shock in neonates will reduce morbidity and mortality.

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MEAN PLATELET VOLUME IN PRETERM INFANTS ADMITTED TO THE NEONATAL INTENSIVE CARE UNIT

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Purpose of study Platelets have an important role in both coagulation and in modulation of inflammation. Mean platelet volume (MPV) is often used as an indicator of platelet function, with larger platelets being more reactive. Studies have shown that MPV measured in the first 24 hours was higher or not different in infants with and without bronchopulmonary dysplasia (BPD). There is very little data in the preterm

population regarding MPV values. The purpose of the study is to describe reference values for MPV in a population of premature infants (≤32 weeks) admitted to the NICU.

Methods used In this retrospective cohort study, we included infants admitted to LAC+USC Medical Centre NICU with a gestational age (GA) of ≤32 weeks. Platelet count and MPV measurements were done using a UniCel DxH Series Workcell Coulter Cellular Analysis System. These values were collected in the first 24 hours as well as information regarding birth weight, GA, and other demographic data. Our data were analysed in two subgroups based on the GA of 23 0/7–27 6/7 weeks (extremely preterm infants) and 28 0/7–32 6/7 weeks.

Summary of results 177 patients had measurements of platelet count and MPV. The subgroup of patients <28 weeks (n=85) with a GA of 25.2±1.3 weeks, birth weight 751±219 g, female (48.2%), Hispanic (62.4%) had a platelet count of 209 ±68 × 10³/mm³ and MPV of 8.1±0.7 fL (Mean ±SD). The other subgroup of patients 28–32 6/7 weeks (n=92) with a GA of 29.5±1.3 weeks, birth weight 1181±225 g, female (56.5%), Hispanic (75%) had a platelet count of 213±67 × 10³/mm³ and MPV of 8.3±0.9 fL.

Conclusions The MPV in premature infants (especially extremely preterm infants) is equal to, or slightly higher than the reference values reported in term infants. More studies are needed to establish normative data for MPV in extremely preterm infants who are at risk for developing BPD.

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LEVEL OF TRAINING AND LUMBAR PUNCTURE SUCCESS IN A MULTICENTER ACADEMIC NEONATAL INTENSIVE CARE UNIT

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10.1136/jim-2017-000663.337

Purpose of study Lumbar puncture (LP) is a commonly-performed procedure in neonates and infants. Traumatic and unsuccessful lumbar punctures are difficult to interpret, leading to repeat procedures, patient discomfort and potentially unnecessary antibiotic use. Studies vary in regard to whether level of training has an effect on LP success rate, however, educational efforts primarily focus on improving resident skills.

Methods used A 5 year retrospective chart review was conducted of all patients who underwent LP between January 2011 to December 2015 at two academic affiliated NICUs.

Summary of results A total of 661 LPs were performed on 529 patients. The LP was a dry tap in 21.2% of all LPs. Multiple providers performed LPs on patients in the NICUs; 45.4% by Residents, 14.8% by NICU Fellows, 35.4% by Neonatal Nurse Practitioners (NNPs), and 4.3% by practitioners in the Emergency Department (ED). Among all providers, the likelihood of obtaining CSF is highest among the NNPs (OR=2.6) and lowest among the ED physicians (OR=0.25) (table 1).

Conclusions The majority of the LPs are performed by the residents in these academic NICUs, but their likelihood of successfully obtaining CSF is no different either as a dry tap or traumatic LP. The ED physicians had the least exposure to LPs and the lowest success rate in obtaining CSF. Increased simulation training or use of ultrasound guidance may improve exposure as well as success rate in the NICU and the ED.

Abstract 337 Table 1 CSF obtained by provider

Provider	Dry n=141	CSF (n=520)	Odds Ratio (OR)	95% confidence	p=value
ED (%)	12 (8.5)	12 (2.3)	0.25	0.11–0.57	0.001
Resident (%)	62 (44)	192 (37)	0.74	0.51–1.08	0.264
Fellow (%)	13 (9)	70 (14)	1.5	0.83–2.8	0.180
NNP (%)	23 (16)	175(34)	2.6	1.6–4.2	<0.001

338 INDICATION FOR LUMBAR PUNCTURE IN NEONATES DURING THE FIRST WEEK OF LIFE

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Purpose of study Although indications for sepsis evaluation in the newborn are well documented in the literature, it is unclear if and what level of elevated C-reactive protein (CRP) in an asymptomatic neonate is an indication for lumbar puncture (LP). The purpose of this study was to evaluate the reasons for LP in the first week of life in neonates admitted to our Neonatal Intensive Care Unit (NICU) due to abnormal labs or clinical signs of sepsis.

Methods used A 5 year retrospective chart review was conducted on patients who underwent LPs in the first week of life between January 2011 to December 2015 at a single level 3 academic NICU. Indication for LP was classified into 4 groups. Group 1 were asymptomatic neonates with positive blood cultures, Group 2 were asymptomatic neonates with abnormal labs, Group 3 were symptomatic neonates with abnormal labs, and Group 4 were symptomatic neonates with normal labs.

Summary of results A total of 251 LPs were performed on infants in the first week of life. Eight percent of the procedures were performed in Group 1, 26.3% in Group 2, 46.6% in Group 3, and 19% in Group 4. Asymptomatic neonates with abnormal labs had LP performed within the first postnatal day compared to other groups ($p=0.011$). The median CRP value among the groups, was highest among those who had culture positive sepsis with clinical symptoms. There was no significant difference in the CSF leukocyte count among the groups ($p=0.47$). Almost 30% of the LPs were unsuccessful and almost 50% of the LPs were traumatic (>500 red blood cells); however, these were not statistically different between the groups.

Conclusions The most common indication for LP in the first week of life was clinical symptoms with abnormal laboratory values including positive blood culture. Highest CRP was seen in asymptomatic patients and symptomatic culture positive sepsis. Despite these elevated CRP values, there was no correlation with leukocytes in the CSF. Additionally, quality improvement measures should be initiated to decrease the high number of unsuccessful and traumatic LPs.

Nephrology and hypertension

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

339 AUTOPHAGY INDUCERS INCREASE AUTOPHAGIC FLUX IN POLYCYSTIC KIDNEY DISEASE (PKD)

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10.1136/jim-2017-000663.339

Purpose of study Autophagy is an essential physiological process that repairs damaged cells by recycling damaged proteins and organelles. Autophagic flux, the fusion of autophagosomes with lysosomes and subsequent degradation of damaged cargo, is the best measure of autophagy. To measure autophagic flux, mice are treated with the lysosomal inhibitor, bafilomycin (BAF) and LC3-II, the best marker of autophagosomes, is measured. If the increase in LC3-II is due to increased autophagosome production then Baf will further increase LC3-II. If the increase in LC3-II is due to a lysosomal defect, then BAF would not affect LC3-II. Thus, lack of an effect of BAF suggests a defect in autophagic flux due to a block of autophagosome lysosomal fusion and degradation. The aim of the study was to determine the effect of known autophagy inducers, 2-deoxy glucose (2DG), trehalose (TRE) and metformin (MET) in PKD1 RC mice (a hypomorphic PKD1 gene knockout) kidneys.

Methods used 90 day old PKD1 RC mice (PKD1^{-/-}) and wild type (+/+) mice were treated for 6 days with either vehicle (Veh), 2DG (100 mg/kg IP), TRE (2% PO) or MET (100 mg/kg IP). After 6 days, a unilateral nephrectomy was performed. Nephrectomized mice were then treated with Baf 1.75 mg/kg/IP and after 2 hours the contralateral kidney was removed (BAF group). LC3-II was measured by immunoblot in kidneys before and after BAF. ATG5 (autophagosome elongation) and ATG4B (autophagosome formation) were measured by immunoblot without BAF.

Abstract 339 Table 1 Immunoblot analysis

LC3-II	+/+	+/+	PKD1	PKD1 ^{-/-}	ATG4B	+/+	PKD1	ATG5	+/+	PKD1
	+	+BAF	-/-	BAF		+	-/-		+	-/-
VEH	+	++	+++	+++	VEH	+	+	VEH	+	+
2DG	+	++	+	+++	2DG	+	+++	2DG	+	+++
TRE			++	++++	TRE	+	+++	TRE	+	+
					MET	+	+++	MET	+	+

Summary of results 1) In +/+kidneys, the amount of LC3-II was increased with BAF suggesting increased autophagic flux. In Veh treated PKD1^{-/-} mouse kidneys, the amount of LC3-II did not increase with BAF suggesting a defect in autophagic flux. 2) TRE and 2DG resulted in an increase in LC3-II in PKD1^{-/-} kidneys. 3) 2DG increased ATG5 in PKD1^{-/-} kidneys.

kidneys, 5) 2DG, Met, TRE increased ATG4B in PKD1 $-/-$ kidneys. See table 1.

Conclusions Autophagic flux is defective in PKD1 $-/-$ kidneys. Autophagy inducers increased autophagic flux in PKD1 $-/-$ kidneys and represent potential therapies.

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NAD⁺-DEPENDENT DEACETYLASE SIRT3 ACTIVATION INHIBITS DIABETIC KIDNEY DISEASE

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Purpose of study Despite interventions for diabetes that seem to have some clinical benefit such as tight glucose and blood pressure control, kidney disease continues to be a problem in many of these patients. Recently mitochondrial dysfunction has been found to play an important role in the pathogenesis of kidney disease. We aimed to test the influence of one key mitochondrial protein deacetylase, Sirtuin 3 (SIRT3), as a potential target for therapy in patients with chronic kidney disease.

Methods used We used kidney biopsies from human patients with and without diabetic nephropathy or glomerulopathy to measure for SIRT3 expression and activity. To test the effect of SIRT3 on the prevention of diabetic kidney disease, we conducted a study comparing three groups of mice: A control group, a diabetic group, and a diabetic group treated with an agonist for SIRT3, nicotinamide riboside (NR). We performed histopathology and immunofluorescence microscopy to visually assess the health of the kidney which included mesangial expansion, glomeruli area, collagen IV expression, and synaptopodin. We also measured for albuminuria, serum triglycerides, SOD2, acetylated lysine, and 4-HNE, all of which are markers for kidney disease progression.

Summary of results SIRT3 expression and activity decreased in human glomeruli and tubules in diabetic patients compared to controls. This result was also shown in diabetic mice compared to controls. Treatment with NR in diabetic mice decreased mesangial expansion, glomeruli area, albuminuria, serum triglycerides, acetylated lysine, SOD2, and 4-HNE compared to control.

Conclusions SIRT3 plays an important role in the progression of diabetic kidney disease. In human renal biopsies SIRT3 expression and activity was decreased in diabetic patients compared to the controls with similar findings in mice as well. Furthermore, markers of kidney disease decreased in treated diabetic mice compared to the untreated diabetic mice. The results of this study show promising results about a potential pharmaceutical target to help prevent the progression of diabetic kidney disease.

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A PHASE I/II, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ASSESSING SAFETY AND EFFICACY OF C1 ESTERASE INHIBITOR FOR PREVENTION OF DELAYED GRAFT FUNCTION IN RECIPIENTS OF DECEASED DONOR KIDNEY TRANSPLANT

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10.1136/jim-2017-000663.341

Purpose of study Delayed graft function (DGF) in kidney allograft recipients is traditionally defined as need for dialysis during the first week after transplantation. DGF is related to ischemia reperfusion injury (IRI) that impacts long-term allograft function and survival. There are no approved therapies for prevention of IRI/DGF. Complement activation induced by IRI may induce DGF. Here we investigate the ability of the complement inhibitor, C1 esterase inhibitor (C1INH) to prevent IRI/DGF in kidney transplant recipients.

Methods used 70 patients receiving cadaver kidney transplants at risk for DGF were randomised to receive C1INH 50 U/kg (35) or placebo (35) intraoperatively and 24 hours later. The primary end point was need for hemodialysis during the first week post-transplant. Assessments of renal function (one year) and dialysis dependency (one month) were accomplished. Complications and safety of therapy was also recorded. Patients were followed for 1 year.

Summary of results Patients randomised to C1INH and placebo exhibited similar characteristics with no significant differences in cold-ischemia time or other risk factors for DGF. C1INH did not result in reduced number of dialysis sessions at 1 week post-transplant, but significantly fewer dialysis sessions ($p=0.0232$) were required 2–4 weeks post-transplant. Patients at highest risk for DGF (KDPI >85) benefited most from C1INH therapy. Significantly better renal function was seen at one year in C1INH treated patients ($p=0.018$). No significant adverse events were noted in the C1INH group.

Conclusions Although the primary end point was not met, significant reductions in the need for dialysis two weeks post-transplant and improvements in long-term allograft function were seen with C1INH treatment. Larger multi-centre trials are needed to confirm these preliminary results.

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CYTOMEGALOVIRUS NEPHRITIS IN A RENAL ALLOGRAFT WITHOUT VIRAL REPLICATION IN BLOOD COEXISTING WITH ACUTE REJECTION

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10.1136/jim-2017-000663.342

Case Report Cytomegalovirus (CMV) is a major pathogen in renal transplant recipients and is associated with major morbidity and mortality as well as allograft rejection. Primary CMV infection occurs in young adults, followed by lifelong latent infection. Reactivation of the virus, more common in the immunocompromised, manifests with variable severity as active CMV infection with CMV replication in the blood and as CMV disease characterised by tissue invasion. The CMV naive allograft recipient by serology (R-) of a CMV positive donor (D+) is at the greatest risk. A recipient with previous CMV infection (R+) is also considered high risk. We report a case of an unusual presentation of CMV in a renal allograft recipient CMV D+/R+ who received induction with basiliximab in conjunction with tacrolimus, prednisone and mycophenolate and CMV prophylaxis with valganciclovir. Five months post transplant a biopsy was performed for a rising creatinine. A BANFF type IIA acute cellular rejection (ACR) was diagnosed. Additionally, an interstitial infiltrate, more prominent than expected with ACR and markedly enlarged tubular epithelial cells with large nuclear inclusions and smaller inclusions in the cytoplasm staining positive for CMV viral antigens

were identified. Repeatedly CMV polymerase chain reaction (PCR) was negative in blood, however upon testing after biopsy, CMV PCR was positive in urine. Renal graft function improved with intravenous gancyclovir, intravenous immunoglobulin and methylprednisolone along with continuation of tacrolimus and mycophenolate. Gancyclovir was followed by oral valgancyclovir. A surveillance biopsy 2 months later revealed continued rejection (treated with methylprednisolone) but no evidence of CMV. However, urine CMV polymerase chain reaction (PCR) remained positive with negative blood PCR for 3 more months indicating active replication of CMV DNA in the graft despite the antiviral therapy. This case illustrates the importance of obtaining urine for CMV PCR if CMV infection or disease is suspected in the renal transplant recipient. A negative PCR for CMV in blood does not exclude CMV disease, which in this setting may be difficult to diagnose.

343 CALCIPHYLAXIS (CALCIFIC UREMIC ARTERIOLOPATHY) IN ESRD PATIENT

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Purpose of study Calciphylaxis is a rare and serious complication of chronic renal failure characterised by vascular calcium overload. It has a high mortality rate. This is a case of systemic calciphylaxis with deep vascular and dermal involvement.

Presentation 38-year-old male with past medical history of uncontrolled diabetes mellitus, hypertension and end stage renal disease, not on dialysis, presented to hospital with two weeks of SOB, productive cough, bilateral lower extremity oedema, diffuse rash on upper and lower extremities and severe penile pain and dysuria.

Hospital Course Diffuse rash turned into tender necrotic eschars. Penile lesion developed into necrotic eschar involving entire glans. Patient developed severe pain in his lower extremities. Plain films of lower extremities revealed severe vessel calcifications. Labs were remarkable for elevated calcium phosphate product and secondary hyperparathyroidism. Management and stabilisation of condition included dialysis, calcimimetics and sodium thiosulfate. Over the course of the next several months, patient underwent penectomy and multiple limb amputations.

Discussion Calciphylaxis was once thought to be a rare complication of ESRD but is becoming more common, possibly secondary to increased recognition of symptoms. The best treatment is not yet known but some ideas include sodium thiosulfate and non-calcium-containing phosphate binders such as sevelamer, cinacalcet for patients with elevated PTH, hyperbaric oxygen, sterile maggot therapy. Pathophysiology is not well understood but clinical manifestations result from reduction in arteriolar blood flow. Medial vessel calcification occurs first. Ongoing vascular endothelial injury causes cutaneous arteriolar narrowing, and hypercoagulable state that causes tissue infarction. Deep vascular involvement will subsequently lead to limb ischemia.

Conclusion Calciphylaxis was once thought to be a rare complication of ESRD but is becoming more common, possibly secondary to increased recognition of symptoms. In this case,

findings included arteriolar calcifications resulting in necrotic skin lesions as well as deep vascular calcifications easily identified with plain films. Clinical suspicion of Calciphylaxis must remain high in ESRD as early diagnosis and intervention can help to avoid amputation.

344 INTRAVENOUS ALBUMIN IS A SAFE AND EFFECTIVE TREATMENT OF OEDEMA IN CHILDHOOD NEPHROTIC SYNDROME

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10.1136/jim-2017-000663.344

Purpose of study Significant morbidity results from oedema in childhood nephrotic syndrome (NS). There are currently no standard guidelines for the use of intravenous (IV) albumin in the treatment of NS-associated oedema. The purpose of this study was to examine in-centre practice variation in dose, frequency and duration of IV albumin infusions, to characterise its effect on weight and to examine frequency of complications.

Methods used A retrospective cohort study was performed for NS patients admitted to BC Children's Hospital from 2000 to 2012 for management of oedema with albumin therapy. We included patients age 1 to 18 years who received $\geq$ one 25% albumin infusion and those with presumed or biopsy-proven minimal change NS. Descriptive data is expressed as mean $\pm$ SD or median(range) as appropriate.

Summary of results 41 patients (17% female) with 52 admissions (age 9.2 ± 5.3 years) and 205 infusions were included. Length of stay was 4.0 (1–27) days. 18 (34.6%) admissions were at NS initial presentation. Number of infusions per day was 1.0 (0–2). Total number of infusions per admission was 3.0 (1–16). Albumin dose per infusion was 0.9 ± 0.2 g/kg. Infusion duration was 169.1 ± 40.8 min. First dose of furosemide was at 80 (0–235) min into infusion. The group with higher infusion density (infusions/length of stay >1.0 /day) had weight loss of 7.8(–5.1–16.7)% and the group with lower infusion density (≤ 1.0 /day) had weight loss of 5.2 (0–26)% ($p=0.755$). There was a transient increase in systolic BP (sBP) to a maximum of 2.5(–18–38)% at 2 hour into the infusion; however, sBP returned to baseline by 4 hour (0.0(–25–19)% change). From first to last serum creatinine, there was a 14.8(–30–183)% increase in eGFR. Only 3 (5.8%) admissions had suspected pulmonary oedema on x-ray.

Conclusions We found significant practice variation in the use of IV albumin for treatment of oedema in NS. Treatment was effective with a significant degree of weight loss achieved with high and low infusion density. Safety is supported by no sustained increase in blood pressure, improved renal function and few cases of pulmonary oedema. With these results, our next goal is to standardise practice regarding use of albumin for NS-associated oedema at our centre.

345 PRACTICE VARIATION IN THE USE OF STEROID-SPARING AGENTS IN CHILDHOOD NEPHROTIC SYNDROME

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10.1136/jim-2017-000663.345

Purpose of study Most children with nephrotic syndrome (NS) respond to prednisone; however up to 80% will have recurring relapses necessitating repeated therapy. Several steroid-sparing agents (SSAs) can be used to minimise relapses, thereby reducing steroid exposure and toxicity. However, standardised clinical pathways (CP) for the use of SSAs in childhood NS are lacking. We hypothesised that practice variation in the use of SSAs exists and affects clinical outcomes.

Methods used This was a retrospective cohort study of NS cases diagnosed at BC Children's Hospital between 1990–2017 and started on an SSA. We excluded patients with secondary NS, age <1 year at diagnosis, and steroid resistance before SSA use. Outcome measures included number of SSAs used and SSA daily dosing. Numbers of relapses before, during, and after SSA use were defined, and annualised relapse rate (ARR) was calculated as number of relapses/years of follow-up.

Summary of results A total of 63 patients received 160 SSA treatments (median 2 per patient). Median age at diagnosis was 3.5 years, 35% (22/63) were female, and 80% (50/63) had a frequently relapsing course prior to SSA use. Cyclophosphamide (CPM) was the most commonly used SSA (29% of all treatments). When used as a first SSA, CPM reduced the median ARR from 7.6 to 1, while MMF reduced the median ARR from 5.4 to 0. Calcineurin inhibitors were more commonly used as second or third (or later) SSAs, with reductions of median ARRs from 5.4 to 3.4 and 3.4 to 2.4 respectively. SSA dosing varied significantly with CPM being given as 2 mg/kg/day (range 1–3.8), MMF as 1020 mg/m²/day (range 250–1485), and cyclosporine as 4.6 mg/kg/day (range 1.6–8.2). This dosing variation impacted on outcomes. With CPM, cumulative doses in the lowest quartile (<115 mg/kg) were associated with a significantly higher subsequent median ARR than the rest of the cohort (4.2 vs 1, $p=0.04$).

Conclusions Significant practice variation exists for the use of SSAs in NS. In the case of CPM, the most commonly used first SSA, lower CPM exposure (ie lower cumulative dose) led to higher relapses. Results from this study reinforce the need for standardised clinical care and will help guide future iterations of our NS CP.

Neuroscience II

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

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INVESTIGATION OF THE EFFECT OF LATENT TOXOPLASMA GONDII INFECTION ON STRIATAL NEURODEGENERATION IN THE YAC128 MOUSE MODEL OF HUNTINGTON'S DISEASE

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Purpose of study Huntington's disease (HD) is a progressive neurodegenerative disease caused by a CAG repeat expansion in the huntingtin gene. The size of the CAG expansion inversely correlates with age of HD onset. However, there is

significant variability in the age of onset attributed to genetic factors and environmental modifiers. One possible environmental modifier of HD progression may be infectious diseases. *Toxoplasma gondii* (*T. gondii*) is a latent (clinically silent) neuroinvasive protozoan parasite. We have previously demonstrated that HD mice have an altered response to *T. gondii* and that latent infection results in significantly decreased brain weight. The striatum is a primary site of degeneration in HD. The purpose of this study was to determine if *T. gondii* induced striatal atrophy in HD mice using the YAC128 mouse model.

Methods used HD and wild-type mice were infected with 10 *T. gondii* cysts by oral gavage at 2 months. Mice were sacrificed at 12 months of age by cardiac perfusion with 4% paraformaldehyde fixative, brains sectioned at 40 µm, then mounted and stained using the Nissl method. Striatal volume and neuronal numbers were quantified using un-biased stereology and slides were blinded to the evaluator.

Summary of results Striatal volume was significantly decreased in HD mice compared to wild-type mice in the absence of infection ($p=0.0339$). Infected HD mice had a significant decrease in striatal volume compared to both non-infected HD ($p=0.0015$) and infected wild-type control mice ($p<0.0001$). Infected HD mice had significantly fewer striatal neurons compared to non-infected HD mice ($p=0.0391$) as well as infected wild-type mice ($p=0.0292$).

Conclusions We demonstrate an altered response to neuroinfection with latent *T. gondii* in YAC128 HD mice versus wild-type mice. YAC128 HD mouse striata are specifically vulnerable to the effects of latent *T. gondii* infection. This work demonstrates the disease-modifying potential of environmental factors, such as chronic infection, in HD progression. Further work is needed to determine if and how chronic infection impacts human disease.

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A PERPLEXING PRESENTATION OF PITUITARY APOPLEXY

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10.1136/jim-2017-000663.347

Case Report Pituitary apoplexy is rare and is characterised by headache, ophthalmoplegia, vision loss, and pituitary insufficiency. Signs of meningeal irritation are rare. We present a patient with apoplexy who presented with meningeal symptoms.

A 59 yo male presented with headache, stiff neck and nausea, but denied rhinorrhea, rash, penile discharge or recent travel. Past history included 2 similar presentations, 21 months and 1 month prior, with CSF showing neutrophilic pleocytosis, and CT scan showing a prominent pituitary gland. He was treated empirically for bacterial vs viral meningitis on both occasions. Seventeen months prior, a non-functioning pituitary macroadenoma was identified requiring hormone replacement, but surgical resection was not performed. Upon current presentation, vital signs were stable and physical exam was remarkable for nuchal rigidity. MRI showed an expansile pituitary gland lesion measuring 2.0 × 1.7 × 1.5 cm with upward displacement of the overlying optic chiasm. CSF again showed neutrophilic pleocytosis, low glucose, high protein content, and cultures were negative. The patient then underwent transphenoidal hypophysectomy, with pathology showing necrotic

tissue indicative of apoplexy. Post-operative CT scan showed complete resection of the tumour. Discharge medications included hydrocortisone, levothyroxine and testosterone.

Apoplexy resulting from ischaemic or haemorrhagic necrosis of the pituitary has an incidence of 1%–26% of pituitary tumours. Signs of meningeal irritation, indistinguishable from infectious meningitis, are rare. Prior reports indicate a few cases where apoplexy presented with sterile meningitis attributed to expulsion of necrotic material or other substances into the suprasellar subarachnoid space. Pituitary apoplexy is a serious condition with a mortality risk as high as 12.5%. This case was exceptional because he did not exhibit classical apoplexy findings, but presented with meningeal symptoms. Diagnosis of pituitary macroadenoma was delayed until the patient developed symptoms of ACTH and thyrotropin insufficiency. Early identification of apoplexy masquerading as meningitis with early surgery may prevent complications, recurrence, and morbidity. Thus, sterile meningitis in patients with a known pituitary adenoma should be considered for prompt surgical intervention.

348 EFFECTS OF IL-34 ON MACROPHAGE PHENOTYPE IN RESPONSE TO AMYLOID-BETA CONFORMERS ASSOCIATED WITH ALZHEIMER'S DISEASE

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Purpose of study Interleukin-34 (IL-34) acts as a second ligand to the macrophage colony-stimulating factor (M-CSF) receptor but appears to trigger distinct innate immune responses. Increasing evidence indicates a key role for peripheral monocytes and macrophages in the clearance of cerebral amyloid-beta (A β), a major risk factor for Alzheimer's disease (AD). Here, we investigated the effects of IL-34 on the differentiation of monocytes into functional macrophages, their immunological profile, and their ability to resist synaptotoxic A β ₄₂ forms pathognomonic to AD.

Methods used We characterised murine bone marrow-derived monocyte/macrophage (Mo/M Φ) primary cultures with media containing M-CSF, IL-34, or a regimen involving both cytokines.

Summary of results Monocytes exposed to IL-34 yielded fewer mature macrophages in relation to M-CSF controls, with attenuated attrition rate in Mo/M Φ simultaneously treated with M-CSF and IL-34. IL-34-induced macrophages exhibited less uptake of fibrillar and oligomeric A β ₄₂ than M-CSF-stimulated cells. Expression of TREM2, implicated in A β uptake, decreased in IL-34 groups as compared to M-CSF controls. Also, the surface expression of SCARA-1 bound to A β was reduced in IL-34-cultured macrophages. In accordance, we found diminished expression of MMP-9, an A β -degrading enzyme, in IL-34-treated macrophages. Intracellular compartmentalization of A β to early endosome antigen 1 (EEA1) vesicles was unchanged between M-CSF- vs IL-34-stimulated cells. Macrophage cell morphology was elongated in M-CSF-cultured macrophages, implicating their enhanced pro-healing phenotype as compared to IL-34-treated macrophages.

Conclusions Overall, we demonstrate that exposure to IL-34 during monocyte maturation and differentiation affects

macrophage phenotype and reduces their ability to eradicate pathological A β forms associated with AD. Future studies should investigate how IL-34 may impact brain-resident microglia and infiltrating macrophages, which may contribute to the development of AD.

349 A CASE OF ANTI-LEUCINE-RICH-GLIOMA-INACTIVATED (LGI1) LIMBIC ENCEPHALITIS REFRACTORY TO TREATMENT

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Purpose of study Anti-LGI1 limbic encephalitis is a rare form of autoimmune disease with a unique presentation including cognitive disorder, seizure, hyponatremia and behavioural changes. Intravenous Immunoglobulins and plasma exchange are main treatment modalities. LGI1 is a secreted neuronal protein that interacts with presynaptic and postsynaptic receptors, and mutations of LGI1 have been associated with the syndrome of autosomal dominant lateral temporal lobe epilepsy. Seizures associated with Anti-LGI1 limbic encephalitis usually improve with immunosuppressant drugs but often do not respond to anticonvulsants alone. The purpose of this case report is to illustrate a difficult case of LGI1 limbic encephalitis refractory to treatment.

Methods used Retrospective chart review.

Summary of results This is a previously healthy 47-year-old Hispanic female who presented to our emergency department with several episodes of tonic-clonic and fasciobrachial seizures, confusion, hyponatremia, visual and auditory hallucinations, urine and bowel incontinence, psychosis, and decreased ability to perform her daily activities. Clinical suspicions for autoimmune encephalitis were made but her entire work up, such as brain MRI, CT chest/abdomen/pelvis, TB, Coccidioidomycosis, SLE, Hepatitis, HSV-1, and Sjogren were all unremarkable except for oligoclonal bands present in CSF and serum. A serum autoimmune encephalitis panel was sent to the University of Pennsylvania and found to be positive for the LGI1 antibody. Following treatment guidelines, intravenous immunoglobulin for 5 days, six courses of plasmapheresis, rituximab, cyclophosphamide, and mycophenolate mofetil were used sustainable improvement over more than a year course of her disease. At last, a 5 day course of high dose methylprednisolone subsided her symptoms.

Conclusions To the best of our knowledge, this is a rare case of Anti-Leucine-Rich-Glioma-Inactivated Limbic Encephalitis that responded successfully to high dose methylprednisolone refractory to all other treatment modalities.

350 ABERRANT PURKINJE CELL FIRING IN A PRRT2 KO MODEL OF PAROXYSMAL KINESIGENIC DYSKINESIA

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10.1136/jim-2017-000663.350

Purpose of study Paroxysmal kinesigenic dyskinesia (PKD) is a movement disorder characterised by the onset of dystonia following sudden movements. PKD is most commonly caused by mutations in the *PRRT2* gene. *PRRT2* is a known interactor with SNAP-25, a component of the presynaptic vesicular

release complex SNARE, where it has been suggested to play a role in calcium sensing. It is unknown how PRRT2 mutations could affect neural circuits to produce dystonia, however, a common theme in dystonic animal models is slowed and irregular firing of cerebellar Purkinje cells (PCs). We hypothesise that PRRT2 KO causes impaired short-term facilitation at parallel fiber-PC synapses leading to slow and irregular PC firing.

Methods used P7-P21 mice were anaesthetised, transcardially perfused with Tyrode's solution, and decapitated. Cerebella were removed and sliced coronally at 300 µm on a Leica VT1000S Vibratome, then incubated in oxygenated Tyrode's solution at 37°C for 1 hour and placed at RT. Whole-cell recordings of PCs were taken using 2–4 MΩ pipettes filled with potassium gluconate internal solution. Parallel fibres were stimulated with a twisted steel electrode placed in the cerebellar cortex. Post hoc genotyping of tail snips was performed at the University of Tennessee Health Science Centre.

Summary of results Recordings of PCs while stimulating parallel fibres revealed short-term facilitation defects in *Prprt2*[±] mice as indicated by the ratio of the 1 st to nth iEPSC (genotyping revealed no *Prprt2*^{-/-} animals in these experiments). PC firing in *Prprt2*^{-/-} and *Prprt2*[±] mice is slower both spontaneously and with injected current steps relative to WT controls. Additionally, PC firing occurs in irregular bursts of action potentials riding on broader, calcium-like spikes in KO animals.

Conclusions PRRT2 deletion causes alterations firing properties of PCs. The pattern of PC firing suggests a defect in the regulation of calcium currents. Our results also demonstrate short-term facilitation defects at the parallel fiber-PC synapse, however it is unknown how or whether this synaptic deficit could lead to the altered properties of PCs we observe. Further experiments isolating PCs with receptor antagonists will allow us to parse out whether this activity is inherited from synaptic malfunction or is intrinsic to PCs.

351 NEURONAL SUPPLEMENT DEPRIVATION DECREASES ERYTHROPOIETIN RECEPTOR EXPRESSION IN MOUSE BRAIN AND SPINAL CORD NEURONS IN-VITRO

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10.1136/jim-2017-000663.351

Purpose of study The tissue protective receptor (TPR), a heterodimer of β- common receptor (BCR) and erythropoietin receptor (EpoR), triggers a tissue protective mechanism in neurons. An *in-vitro* model of neuronal ischemia requires oxygen and glucose deprivation (OGD). OGD experiments on neonatal mouse neurons revealed a large decrease in EpoR, which may not be due to the OGD conditions. Serum free neuronal culture commonly uses neuronal supplement (NS) B27. It is not present in OGD treatment media to avoid alteration of ischaemic damage. We hypothesise that the deprivation of neuronal supplement independently reduces EpoR present on the neuronal cell membrane.

Methods used Brain and spinal cord tissue was collected from neonatal mice (2–5 days old), then digested by papain and trituration. Neurons were isolated from the digested tissue by centrifugation. The neurons were cultured at a density of 200 k–250 k cells/cm² for 1 week on PDL coated plates in Neurobasal-A Medium with 2% (v/v) B27 neuronal

supplement (Gibco). The cells were then treated with either B27 deprived media or fresh media with 2% B27. After 1–2 hours, the cells were lysed and a Western blot for BCR and EpoR was performed.

Summary of results Neurons subject to NS deprivation showed decreased EpoR such that it was undetectable relative to neurons given 2% B27 (brain: 0.0 vs 0.39±0.055, p<0.01; spinal cord: 0.0 vs 0.33±0.056, p<0.01). BCR was not significantly different in neurons deprived of NS versus neurons given 2% B27 (brain: 0.45±0.046 vs 0.46±0.044, p=0.91; spinal cord: 0.35±0.056 vs 0.32±0.051, p=0.74).

Conclusions Neuronal supplement deprivation reduces the amount of EpoR present on neurons, while having no effect on BCR. This may imply that EpoR is required at some ratio to facilitate BCR's protection mechanism. Future study aims to better define the relationship between EpoR and BCR, and their tissue protective mechanism. In addition, effects of a decrease in TPR should be considered when using this *in-vitro* model.

352 GPR143 AND DOPAMINE SIGNALLING CONTROL LYOSOMAL ACTIVITY IN RETINAL PIGMENT EPITHELIAL CELLS

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10.1136/jim-2017-000663.352

Purpose of study Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. While the aetiology of AMD is complex, a link between retinal pigment epithelium (RPE) pigmentation and retinal health is likely. RPE receptor GPR143 is a G-protein coupled receptor that participates in the pigmentation pathway with its ligand L-DOPA. Dopamine receptors in the RPE participate in a mechanism that involves engulfing and digesting outer segments of spent photoreceptors. One outcome of dopamine receptor signalling in the RPE is a pH decrease in the lysosomal compartment where outer segments are degraded. In this study, we tested the hypothesis that GPR143 signalling impacts RPE degradative capacity, akin to signalling by dopamine receptors, by shifting traffic to the lysosome.

Methods used We utilised bovine eyes harvested closely after euthanasia. After dissection, both RPE and choroidal melanocytes were collected and plated in tissue culture vessels. The lysosomal compartments were visualised using a lysosensor, a pH-sensitive dye in which the emissions change relative to pH. L-DOPA or dopamine were added to 1 µM and images were captured by confocal microscopy over a 20 min time course. The fluorescence intensity was measured in response to drug, with no drug treatment as the negative control. At the end of the time course we used a low pH standard buffer to permeate the cells and achieve maximum signal intensity for each cell.

Summary of results Our results illustrate variability of dye uptake both between and within cell types. In melanocytes we observed discrete organelles the expected size of lysosomes. In RPE *in-situ* preps we observed discrete organelles resembling lysosomes, but we also noted prevalent diffuse fluorescence. This was likely due to the difficulties of using light microscopy in heavily pigmented, polarised epithelium in which pigment granules are apically distributed. Using *in-situ* RPE preps, L-DOPA and dopamine both caused an increase in

fluorescence in the basal regions. In contrast, a decrease in fluorescence of the lysosomal compartments with both L-DOPA and dopamine was observed in melanocytes.

Conclusions Our results suggest L-DOPA causes an increase in lysosomal activity in RPE, but that the relationship of L-DOPA and dopamine to lysosomal activity may be cell-type dependent.

353 SORSBY FUNDUS DYSTROPHY: THE ROLE OF THE S181C MUTATION IN TISSUE INHIBITOR OF METALLOPROTEINASE 3 IN EXTRACELLULAR MATRIX REMODELLING

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10.1136/jim-2017-000663.353

Purpose of study Sorsby Fundus Dystrophy (SFD) is a disease similar to age-related macular degeneration (AMD) and results from a mutation in the retinal pigment epithelium (RPE)-expressed endopeptidase tissue inhibitor of metalloproteinase 3 (TIMP3). TIMP3 inhibits matrix metalloproteinases (MMPs) and plays a role in extracellular matrix (ECM) and Bruch's membrane (BM) remodelling. In SFD patients there is a dysregulation of ECM remodelling and Sorsby eyes demonstrate an abnormal accumulation of basolaminar deposits. The purpose of this study is to evaluate whether RPE generated from the induced pluripotent stem cells (iPSC) of Sorsby patients demonstrate a similar phenotype to their *in vivo* counterparts.

Methods used Control iPSC-RPE generated from three unaffected family members and iPSC-RPE generated from two subjects from the same family with the S181C TIMP3 mutation were analysed. Donated globes from affected members of the same family were used for histological analysis. Histological staining was used to identify the anatomy of BM deposits in SFD eyes compared to AMD and normal age-matched controls. The composition of SFD deposits was determined using immunohistochemistry. Transmission electron microscopy (TEM) imaging of SFD iPSC-RPE was performed. Western blot analysis, zymography, and reverse zymography were used to characterise the expression and activity of mutant TIMP3.

Summary of results Histology of SFD eyes revealed that the thickened BM is comprised of TIMP3, vitronectin, APCS, and ApoE. TEM imaging of SFD RPE *in vitro* indicates that these deposits share the same structural components as basal laminar deposits seen in SFD patients. There was a significant increase in TIMP3 expression in SFD RPE compared to controls, although there was no corresponding increase in MMP inhibition. This implies that S181C TIMP3 is a less effective inhibitor of MMP activity compared to wild type.

Conclusions Sorsby Fundus Dystrophy globes demonstrate thickened BM that is composed of increased TIMP3 expression, vitronectin, APCS, and ApoE compared to controls. Our

SFD iPSC-derived RPE demonstrate significantly greater accumulation of ECM deposits. We demonstrate that S181C TIMP3 is a less effective inhibitor of MMPs, which may result in increased ECM deposition.

Surgery IV

Concurrent session

Friday, January 26, 2018

10:15 AM – 12:30 PM

354 APPLYING SWOT ANALYSIS TO THE ACGME SELF STUDY CAN HELP PROGRAMS ARTICULATE STRATEGIES FOR IMPROVEMENT: A PILOT TRIAL IN A PLASTIC SURGERY RESIDENCY

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10.1136/jim-2017-000663.354

Purpose of study In 2013, the ACGME launched the Next Accreditation System with goals to help programs implement strategies for continuous improvement. To that end, the ACGME Self Study is designed to engage programs in defining aims, identifying opportunities for improvement, and tracking outcomes. Initial tests of the ACGME Self Study showed that programs could clearly articulate aims but had more difficulty articulating ongoing efforts for development. The purpose of this study is to show how a SWOT (strengths, weaknesses, opportunities, threats) analysis results in practical and relevant strategies for improvement. This study was done as part of the Self Study at the Department of Plastic Surgery of Loma Linda University.

Methods used A Self Study committee prepared a survey listing relevant internal and external factors of success. All program faculty and residents participated. Participants ranked their own top factors in each SWOT category but took the survey together so they could discuss ideas and add their own factors to the survey. The survey results were aggregated using a sum reverse score.

Summary of results The bottom five scores from the strengths and opportunities categories along with the top five scores from the weaknesses and threats tabs were collated (figure 1). These were then used to form the basis of work groups consisting of faculty and residents to create strategies to improve performance in these areas. Several specific strategies were defined in this analysis.

Conclusions As residency programs approach their ACGME Self Study, a SWOT analysis may provide a valuable assessment and guide performance improvement strategy development.

STRENGTHS	SCORE	RANK	COUNT
Research within the department	8	14	2
Scholarly activity (publications, dissemination of publications at meetings)	6	15	1
Collaborative learning environment with other departments and midlevel providers	6	15	1
Changes brought on by new site, faculty, or residents	4	17	1
Simulation training and simulation exercises focusing on specific skills	2	18	1
WEAKNESSES	SCORE	RANK	COUNT
Collaborative learning environment with other departments and midlevel providers	67	1	8
Simulation training and simulation exercises focusing on specific skills	43	2	5
Missing specific educational experiences or case types (e.g. required burn rotation)	41	3	5
All areas at or below 70% on ACGME resident or faculty survey	41	3	6
Scores on in-training exam falling or at 30th percentile	34	5	4
OPPORTUNITIES	SCORE	RANK	COUNT
Specific effects of number of sites or specific site	16	9	2
Specific faculty issues (teaching, supervision, unprofessionalism, manpower)	10	10	1
Disturbing scores on ACGME resident or faculty survey	7	11	1
Opening of fellowships at home institution to retain talent within	7	11	1
Loss of other residencies	6	13	1
THREATS	SCORE	RANK	COUNT
Disturbing scores on ACGME resident or faculty survey	74	1	8
Opening of fellowships at home institution to retain talent within	46	2	6
Adverse publicity about the program	41	3	5
Instability in faculty or leadership	37	4	4
Failure to use program evaluations to improve program	36	5	4

Abstract 354 Figure 1 The bottom five scores from the strengths and opportunities categories along with the top five scores from the weaknesses and threats tabs were collated.

355 REGULATION OF TENDON HEALING IN ADULT MICE

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10.1136/jim-2017-000663.355

Purpose of study Tendons are specialised dense tissues that connect muscle to bones and play a critical role in locomotion of the human skeleton. Tendon injury can occur as a result of acute trauma, overuse and/or insidious tissue degeneration due to ageing. At the present time, we know little about how tendon injury is repaired. The purpose of this study is to develop a mouse model of tendon injury relevant to human disease using ESET (ERG-related protein with a SET domain), a histone methyltransferase that has been previously identified to play a role in the regulation of tendon formation during embryonic development.

Methods used Conditional knockout (CKO) of ESET in adult mice was achieved through the Cre-LoxP system and intraperitoneal injection of tamoxifen one month prior to starting physical exercise. 10 month-old WT and CKO mice then underwent a 30 min daily treadmill regimen at 10–12 metre/min and 10° incline to simulate joint overuse. After days 14 and 21, mice were euthanized and patella tendons were isolated for biomechanical characterisation via tensile strength

testing (stretched at a rate of 0.5 mm/second until failure). Immunohistochemistry (IHC) characterisation was performed at days 14 and 21 to assess for morphological changes in the patella tendon. RT-PCR was performed using RNA from WT and CKO tenocytes to analyse for changes in tendon-related genes.

Summary of results After 14 days of running, the average tensile strength of WT patella tendon was 10.04 ± 2.37 Newton (N) and the average for CKO patella tendon was 8.25 ± 1.52 n (T test, $p=0.049$). When male mice were analysed separately, the decrease in tensile strength was more profound (11.49 ± 0.55 n in WT and 8.46 ± 1.09 n in CKO; T test, $p=0.003$). ESET mRNA was undetectable in CKO tenocytes. No difference in expression of tenocyte-related genes scleraxis and COL1A1 was detected in CKO vs WT tenocytes. However, the expression of tenomodulin and tenascin C was found to be significantly reduced in CKO tenocytes. Tensile testing at day 21 and IHC characterizations are in-progress.

Conclusions Through this pilot study, we found that ESET is critical to the tensile strength of patella tendon in adult mice, likely due to ESET regulation of specific tendon genes tenomodulin and tenascin C. Future studies aim to expand this pilot study and investigate epigenetic mechanisms underlying ESET regulation.

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TEACHER-LEARNER CONTRACT (TLC): AN OBJECTIVES-BASED CHECKLIST FOR SURGICAL SHADOWING

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Purpose of study Shadowing is an important way for first- and second-year medical students to explore different specialities, connect with mentors, and develop clinical skills. However, its informal nature means that experiences vary greatly and so do the learning outcomes. The Teacher-Learner Contract (TLC) is an objectives-based checklist that was developed as a framework for surgical shadowing.

Methods used 30 student-surgeon pairs were recruited by email. The participants were asked to use the TLC during a single shadowing experience; 28 students and 18 surgeons responded to a post-shadowing questionnaire assessing the TLC's ease of use and general feedback. Thematic analyses of the responses were done using NVivo software.

Summary of results In general, students and surgeons reported that the TLC focused learning and improved communication between teachers and learners. Students also commented that using the TLC prompted them to reflect on their goals and consider how the shadowing experience might contribute to their overall medical education. Quantitatively, both students and surgeons found benefit in using the checklist (mean 3.5 SD 0.745 and mean 3.778 SD 1.06 respectively, where 1 was not useful and 5 was very useful). Both students and surgeons rated the TLC as easy to use, and 80% of respondents said they would use the tool again.

Conclusions The TLC is a useful tool to facilitate meaningful shadowing experiences for teachers and learners and may even have longitudinal impacts.

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VARIATION IN HOSPITAL COSTS FOR GASTROSCHISIS CLOSURE TECHNIQUES

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10.1136/jim-2017-000663.357

Purpose of study Gastroschisis (GS) is a congenital anomaly that requires an emergent surgical intervention in the newborn to reduce the viscera and repair the abdominal wall. There are currently three accepted ways to repair GS: 1) primary fascial closure; 2) primary umbilical cord closure; 3) delayed fascial closure with initial silo placement. All three techniques are considered safe with similar outcomes although cost differences have not been explored. The purpose of this study was to investigate differences in total hospital costs between GS closure techniques.

Methods used A retrospective review was performed of newborns admitted to Seattle Children's Hospital with GS from 2011 to 2017. Demographic data and factors that contributed to hospital cost of GS during the initial hospitalisation were collected. Inflation adjusted cost data were obtained through the hospital's Clinical Standard Work GS pathway. Differences between procedure cost, hospital stay, and feeding endpoints were analysed using multivariable linear regression adjusting

for prematurity, complicated GS, and performance of other operations unrelated to GS. P-values were adjusted using False Discovery Rate across models for each variable.

Summary of results 88 patients with GS were identified during the study period. 14%, 65%, and 21% underwent primary fascial, primary umbilical cord closure, and delayed closure, respectively. Delayed closure increased total hospital costs by 57% compared to primary closure using the fascial or umbilical cord techniques ($p < 0.001$). Delayed closure was also associated with increases in total length of stay ($p < 0.05$), NICU stay ($p < 0.001$), parenteral nutrition duration ($p < 0.05$), ventilator days ($p < 0.001$), time to goal enteral feeds ($p < 0.05$), and all inpatient cost categories except standard medical room cost ($p < 0.001$). Total hospital costs were increased by 47% in infants who required operations in addition to GS closure ($p < 0.001$).

Conclusions Delayed closure for GS and the need for additional operations were associated with significant increases in total hospital cost during the index admission. As GS is a costly and resource-intensive congenital defect, identifying the most cost-effective technique to repair GS may reduce excess spending in children's hospitals.

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PAEDIATRIC POST-APPENDECTOMY SURGICAL SITE INFECTIONS: A RETROSPECTIVE SINGLE-CENTRE STUDY

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10.1136/jim-2017-000663.358

Purpose of study Surgical site infections (SSIs) are a major target for quality improvement projects in surgery. At our site, appendectomies have been found to be an important contributor to our SSI rate. Although the National Surgical Quality Improvement Program (NSQIP) team at BC Children's Hospital (BCCH) has implemented several quality improvement activities that had dramatically decreased post-appendectomy SSI rates, we have recently observed a rise in this adverse outcome. The objective of this single-institution retrospective quality improvement study was to identify factors contributing to the increase in post-appendectomy SSIs in 2016.

Methods used Data abstracts from all institutional appendectomy cases from 2013–2016 included duration of symptoms prior to initial presentation, time from initial hospital assessment to arrival in our ED for transferred patients, elapsed time from ED triage to surgical consultation and from first surgical consultation to appendectomy, and antibiotic administration in compliance with institutional protocols. Outcomes analysed included type of appendicitis (simple versus perforated) and postoperative SSI occurrences. Univariate and multivariate logistic regression analyses were performed.

Summary of results Univariate analysis showed younger age, perforated appendix and longer time span between onset of symptoms to surgery are associated with increased likelihood of SSI. In multivariable analysis only the last 2 variables were independently associated with SSI.

Conclusions This study has identified an opportunity for care improvement for appendicitis, and has resulted in the development of a pathway for expedited diagnosis and treatment.

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PAEDIATRIC SURGERY AND SOCIETY HOW DO HEALTH CARE PROFESSIONALS CHANGE THEIR PRACTICE TO ACCOMMODATE VULNERABLE FAMILIES?

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10.1136/jim-2017-000663.359

Purpose of study An individual's overall health is influenced by their social determinants of health (SDoH), which include: socioeconomic status (SES), transportation, food and housing security, disability and social supports can affect the health outcomes of patients. Low SES is associated with higher rates of infant mortality, higher rates of mental health issues, and poorer adult health outcomes among others. Children from lower income homes are also more likely to receive acute care over preventative care. In British Columbia, 1 in 5 children live in poverty. This study aims to 1. explore how surgeons and medical staff at BCCH modify their care for vulnerable families, and 2. to gather baseline data on families' SDoH.

Methods used This was a survey based study. An ad-hoc questionnaire was developed based on published studies looking at how primary health care providers modify care when treating patients from low SES. The survey was administered to surgeons and medical office staff at BCCH in August 2017. The survey collected data on surgeon and staff's perceptions about SDoH in their patient population, their interventions to lessen the burden of adverse SDoH, and how caring for patients with adverse SDoH influences their practice.

Summary of results Preliminary results showed that surgeons modify the care they provide to accommodate families living with adverse social situations, such as filling out forms free of charge, providing free bandages, and liaising with colleagues in the families' communities. Medical office staff wrote about parents' inability to get time off work, as well as juggling other priorities in the face of adverse economic conditions, as obstacles to the child receiving timely care.

Conclusions Results from this study will be used to inform better intervention and management options for surgical families. Future work is directed at exploring the SDoH in the lives of patients by analysing existing patient databases for demographics, and through direct patient contact. The data will be used to inform interventions to reduce impact of adverse SES and to raise awareness and advocate for vulnerable patients at BC Children's Hospital.

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THE EFFECT OF HEIGHT AND DISTANCE ON RADIATION EXPOSURE FROM FLUOROSCOPY: A BENCHTOP MODEL

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10.1136/jim-2017-000663.360

Purpose of study Fluoroscopy can expose the operating room (OR) personnel to ionising radiation. Distance from the scatter source affects radiation exposure through the inverse square law. As x-rays scatter, radiation diminishes as the distance from the scatter source increases. While studies show there may be an increased risk for brain tumours in surgeons and interventional radiologists that routinely use fluoroscopy, the characterisation of the radiation exposure in surgeons is limited. The purpose of this study was to evaluate the impact of

surgeon height and distance from a scatter source on radiation exposure.

Methods used Fluoroscopic imaging during percutaneous nephrolithotomy (PCNL) was simulated using cadaver models for the patient and surgeon. Radiation exposure to the surgeon's eyes and brain was measured using 8 dosimeters fixed to the eyes as well as the bilateral frontal, temporal, and parietal lobes. The model was exposed to fluoroscopy for 10 min with fixed settings of 90 kVp and 3.8 mAs to reflect standard parameters used in PCNL. Radiation scatter to the surgeon's head was measured at two different heights: 5'2" and 5'10". Five trials were completed at each height with the surgeon model either directly adjacent to the table or 6 inches away. A total of 20 trials were completed.

Summary of results Total radiation exposure was 17.675 mrem at 5'10" compared to 5.675 mrem at 5'2" ($p < 0.001$) at 6 inches from the table. Scattered radiation was higher 6 inches away from the table compared to directly adjacent to the OR table in the left eye (43.4 mrem vs 14.8; $p < 0.001$), left frontal lobe (14.0 vs 8.8 mrem; $p = 0.022$), right frontal lobe (15.4 mrem vs 6.6 mrem; $p < 0.001$), and left temporal lobe (9.8 mrem vs 5.4 mrem; $p = 0.005$). Radiation dose was higher on average in the front four dosimeters compared to the back four (14.265 mrem vs 5.265 mrem; $p < 0.001$). Radiation scatter to the right and left sides of the head were not significantly different ($p = 0.713$).

Conclusions Radiation exposure can change with relatively small changes in distance from the scatter source. Our findings suggest that shorter surgeons and, surprisingly, surgeons that work slightly farther away from the scatter source during fluoroscopic procedures may be at greater risk for radiation exposure to the eyes and brain.

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DO LEAD GLASSES PROTECT THE BRAIN FROM SCATTERED RADIATION IN PERCUTANEOUS NEPHROLITHOTOMY?

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10.1136/jim-2017-000663.361

Purpose of study Intraoperative imaging using radiation is important in many surgical procedures. However, higher incidences of cataracts and brain malignancies have been demonstrated in physicians routinely exposed to radiation. Lead glasses have been shown to protect surgeons' eyes, but it is not known if lead glasses also protect the brain. The purpose of this study was to determine if lead glasses reduce the amount of radiation received by the eye and the cortical lobes.

Methods used A simulated percutaneous nephrolithotomy (PCNL) procedure was set up in an operating room. The patient was simulated using a male cadaver in the supine position on the operating table to model a PCNL patient and a radiation scatter source. The surgeon was simulated using a cadaver head supported on a stand which was placed six inches away from the edge of the operating table at the level of the kidney. To measure the dose of scattered radiation, 8 dosimeters were placed bilaterally in front of the cornea and at the frontal, parietal, and occipital lobes of the cadaver head. A ninth dosimeter was placed on the cadaver patient as a control. The C-arm was set at 3.8 mAs and 90 kVp,

positioned over the patient, and activated for a total of 10 min per trial. Ten trials were conducted: 5 with lead glasses on the cadaver head and 5 without the glasses. Data was analysed using a two-tailed t-test with $p < 0.05$ indicating statistical significance.

Summary of results Lead glasses reduced the dose of scattered radiation to the corneal dosimeters by 62% on the left and 44% on the right (left cornea: 0.054 vs 0.142 mSv $p < 0.01$; right cornea: 0.058 vs 0.104 mSv $p = 0.43$). However, they did not reduce the radiation dose of the frontal, parietal, or occipital lobes (left frontal: 0.03 vs 0.04 mSv, $p = 0.221$; right frontal: 0.03 vs 0.05 mSv, $p = 0.083$; left parietal: 0.02 vs 0.03 mSv, $p = 0.065$; right parietal: 0.04 vs 0.05 mSv, $p = 0.522$; left occipital: 0.01 vs 0.01 mSv, $p = 0.838$; right occipital: 0.02 vs 0.03 mSv, $p = 0.355$).

Conclusions Lead glasses reduced the dose of scattered radiation to the corneas by 62% and 44% on the left and right, respectively, but did not provide protection to cortical lobes from radiation scatter. Because of this, additional measures to protect the brain from radiation may need to be explored.

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DO ILLUMINATED FOOT PEDALS IMPROVE THE SPEED AND ACCURACY OF PEDAL ACTIVATION DURING ENDOSCOPIC PROCEDURES?

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10.1136/jim-2017-000663.362

Purpose of study Endourologic procedures require the use of multiple foot pedals to activate different instruments. Limited working space, surgical drapes, plastic covers, and low-light operating room (OR) settings can risk inaccurate foot pedal activation during these cases. A range of complications can result, including extraneous radiation exposure, accidental cautery, and even patient burns. In fact, OR fires and fatal intra-operative explosions from inaccurate foot pedal activation have been reported. Furthermore, a repetitive search for the correct foot pedal can lead to an increase in operative time with each additional minute costing \$66. The purpose of this study was to evaluate whether the addition of color-coded illumination to conventional foot pedals could reduce error and improve the efficiency of instrument activation.

Methods used Foot pedals for a C-arm, laser, and ultrasonic lithotripter (USL) were positioned randomly in a simulated percutaneous nephrolithotomy. Different coloured glow-sticks were attached to each pedal. Participants were instructed to activate instruments in a randomised sequence with and without illumination. Objective outcomes included time to instrument activation, number of attempted, and incomplete or incorrect pedal presses. Participants also reported subjective preferences regarding pedal illumination.

Summary of results Illuminated pedals decreased average activation time for all instruments collectively (3.95 s vs 6.49 s; $p = 0.017$) and individually (c-arm: 3.07 s vs 4.21 s; $p = 0.006$; laser: 13.04 s vs 15.18 s; $p < 0.001$; USL: 3.28 s vs 4.91 s; $p < 0.001$) compared to non-illuminated pedals. Illuminated pedals also led to fewer attempted presses (33.5 vs 39.5; $p = 0.007$) and incomplete presses (1.5 vs 8.5; $p < 0.001$). The number of incorrect pedal presses decreased but was not significant. Participants reported that illumination simplified pedal activation and recommended its use ($p = 0.01$).

Conclusions Color-coded illumination improved the speed and accuracy of instrument activation. Participants subjectively reported improved efficiency with pedal illumination. The addition of illumination to foot pedals could ultimately improve efficiency and patient safety while simultaneously reducing operative costs.

Joint plenary session

WAFMR, WAP, WSCI, AND WSPR

Friday, January 26, 2018

1:30 PM – 4:30 PM

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INTERACTIVE EFFECT OF DISRUPTIVE GENE EVENTS IN THE β -CATENIN PATHWAY AND MATERNAL AUTOIMMUNITY ON AUTISM SEVERITY

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10.1136/jim-2017-000663.363

Purpose of study Current research supports an interaction between genetic events and environmental stressors in the aetiology of Autism Spectrum Disorder (ASD). There is an enrichment of mutations to genes involved in the β -Catenin pathway, which influences formation of the blood brain barrier (BBB). The BBB excludes antibodies from the brain. Research suggests that maternal autoimmunity increases ASD risk due to the production of brain-reactive antibodies that can cross the placenta and access the brain prior to BBB formation, impacting fetal neurodevelopment. We examined the interactive effect of gene mutations impacting the β -Catenin pathway and maternal autoimmunity on ASD severity.

Methods used Participants included 2759 children with ASD from the Simons Simplex Collection for whom whole exome sequencing, phenotypic characterisation, and medical history were completed. Of this sample, 425 children were selected and grouped based on mutations within the β -Catenin pathway vs outside this pathway, and presence vs absence of a history of maternal autoimmunity. ASD associated symptoms across social, communication, and behavioural domains were extracted from clinician interviews and parent questionnaires. Two-way ANOVAs were conducted to evaluate effects of mutations in the β -Catenin pathway and maternal autoimmunity on ASD symptom severity.

Summary of results Children with gene mutations in the β -Catenin pathway had more severe repetitive behaviour symptoms than children with mutations outside this pathway ($p = 0.005$). A significant interaction was identified indicating that children with mutations in the β -Catenin pathway and a history of maternal autoimmunity show greater ASD severity ($p = 0.011$).

Conclusions These findings suggest that mutations to genes involved in BBB development, when combined with a history of maternal autoimmunity, are associated with increased autistic symptomatology. Our results build on prior work that has shown an association between maternal autoimmunity and ASD as well as the interaction between immune system functioning and mutations and ASD clinical presentation. These observations advance our understanding of the causal mechanisms for this multifactorial disorder.

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REFERENCE INTERVALS FOR CALPROTECTIN IN STOOLS OF PRETERM NEONATES: USING THESE INTERVALS TO EVALUATE SUSPECTED NEC

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10.1136/jim-2017-000663.364

Purpose of study Calprotectin is a granulocyte protein that can be found in stool. Studies by our group and others show higher calprotectin values in stools of neonates with necrotizing enterocolitis (NEC) than in stools of healthy term infants. However, that comparison is flawed because NEC typically occurs in growing premature, not healthy term, neonates. Therefore we created calprotectin reference intervals based on gestational and postnatal age, and evaluated whether a level above the upper reference interval on the new charts is diagnostic for NEC.

Methods used To create proper reference intervals, we measured calprotectin in stools of premature neonates of various gestational and post-natal ages who had no known gastrointestinal pathology. Levels from infants undergoing a 'rule out NEC' evaluation were then plotted on the new charts, and whether or not the infant had NEC was judged by the responsible clinician days/weeks later.

Summary of results Charts based on 249 stool measurements display calprotectin reference intervals on the day of birth according to gestational age and during the first 8 weeks after birth. The 90th percentile exceeded 200 µg/g stool for all gestational and postnatal ages. Levels at birth were lower in those 24–29 weeks gestation at birth than 30–34 weeks gestation at birth ($p=0.007$), and were lower in the first week than in the second through eighth weeks ($p<0.001$). Calprotectin levels during 'rule out NEC' evaluations ($n=118$) were above the reference interval in 59% of those where NEC was documented and in 17% where NEC was judged to be unlikely ($p<0.001$).

Conclusions Stool calprotectin from preterm neonates with no signs of intestinal pathology have a wider range and higher upper reference interval than do stools of healthy children and adults. Among neonates undergoing a 'rule out NEC' evaluation, a stool calprotectin level above the upper interval for age supports the likelihood that the problem is NEC, but this test is not sufficiently specific to independently confirm a diagnosis of NEC.

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EARLY POINT-OF-CARE ULTRASOUND IN CRITICAL CARE: HELPFUL, CRITICAL, OR RECREATING THE SWAN PROBLEM?

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Purpose of study Point-of-care ultrasound (POCUS) has been shown to reduce diagnostic uncertainty and guide therapeutic decisions in critically ill patients. However, data on patient-centred outcomes when POCUS is performed prior to or after key interventions are lacking. The objective of this study was to determine the association between POCUS and outcomes in patients admitted to the ICU from the ED with

haemodynamic instability. Our hypothesis was that POCUS only improves outcomes if performed prior to any interventions to improve haemodynamic instability.

Methods used This was a retrospective case-control analysis of all medical patients admitted to the ICU from two EDs at two academic hospitals from November 1, 2013–October 31, 2016 with shock index >0.6 . Patients were divided into three groups: no POCUS, POCUS before intervention (vasopressor or fluid bolus) or POCUS after intervention. The primary outcome was in-hospital mortality. Secondary outcomes were time to fluids, vasopressors, and intubation. Outcomes were evaluated using appropriate tests for nonparametric distributions.

Summary of results During the study period, 5441 patients met inclusion criteria and were included in the analysis. Of these, 77% (4165) did not receive a POCUS, 11% (614) had a POCUS performed before intervention, and 12% (662) after intervention. Mortality was 22%, 29%, and 26%, respectively ($p<0.001$). Patients with POCUS prior to intervention had a longer median time to fluids (93 min [IQR 42–217]; No POCUS 50 min [IQR 25–118]; POCUS after 40 min [21–78]; $p<0.001$), median time to vasopressor initiation (311 min [IQR 123–793]; No POCUS 252 min [IQR 36–703]; POCUS after 296 min [108–603]; $p=0.002$), and median time to intubation (229 min [IQR 35–740]; No POCUS 90 min [IQR 20–394]; POCUS after 170 min [30–467]; $p=0.001$).

Conclusions These data indicate that critically ill ED patients who had POCUS performed prior to an intervention had an increased mortality and an increased time to administration of vasopressors, fluids, and intubation. These results suggest POCUS should be studied prospectively to further understand its association with outcomes and timing of interventions amongst critically ill patients.

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BRAIN OMEGA-3 METABOLISM IN CARRIERS OF APOE4

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10.1136/jim-2017-000663.366

Purpose of study The purpose of the study is to identify APOE lipidation by the lipid transporter ABCA-1 as a critical mechanism in brain DHA metabolism. Carrying the APOE4 allele is the strongest genetic risk factor for developing Alzheimer's disease (AD). DHA is involved in synapse and memory formation. A role for APOE lipoproteins in DHA brain transport is not known. The ability to form APOE lipoproteins in astrocytes depends on ABCA-1 activity. We previously showed that ABCA-1 activity was lower in cerebrospinal fluid (CSF) of persons with AD compared with cognitively normal individuals.

Methods used We employed cellular, brain imaging and clinical studies to understand how APOE4 regulates the transport of DHA in the brain.

Summary of results Using astrocytes expressing APOE2, APOE3 and APOE4, we demonstrate that APOE4 cells release less DHA into APOE4 lipoproteins compared with non-APOE4 cells. We identify lower ABCA1 activity as a mechanism for the lower DHA release that can be reversed by inducing ABCA-1 activity with an apoE mimetic peptide. To understand the clinical relevance of these findings, we employed PET imaging with ¹¹C DHA in a group of cognitively normal individuals ($n=23$, mean age=37). APOE4

carriers (n=9) had a 30% increase in brain DHA uptake from plasma compared to non-carriers (n=13, $p=0.04$). These findings suggest a DHA deficit in brains of APOE4 carriers. We then examined whether the APOE4 allele affected CSF DHA levels after DHA supplementation. CSF DHA levels of 43 three participants receiving DHA (n=28) vs Placebo (n=15) over 18 months were measured in the ADCS-sponsored DHA trial. Carrying the APOE4 allele was associated with lower increase in CSF DHA levels ($p=0.07$, interaction between genotype and treatment) compared with non-carriers.

Conclusions Our cellular studies identify a novel role for APOE lipidation by ABCA-1 in DHA transport. Decreased ABCA-1 activity in APOE4 cells was associated with a decrease in DHA transport. These findings are clinically relevant as we observed deficits in brain DHA transport in younger cognitively normal APOE4 carriers using DHA PET scans and in APOE4 carriers with dementia after DHA supplementation. Enhancing APOE lipidation using ABCA-1 agonists is a promising strategy to enhance brain DHA metabolism.

Adolescent medicine and general paediatrics III

Concurrent session

Saturday, January 27, 2018

8:00 AM – 10:00 AM

367 CINEMATIC PORTRAYAL OF IMMUNIZATIONS THROUGHOUT HISTORY

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10.1136/jim-2017-000663.367

Purpose of study Anti-vaccination messages are increasingly prevalent in the media. Movies are no exception, as the anti-vaccination film 'Vaxxed' was screened this year at the Cannes Film Festival. As a result, we assessed how films have portrayed immunisation throughout history.

Methods used We identified 16 search terms for vaccines on IMDb (Internet Movie Database). We conducted a search of IMDb with these terms on January 24th, 2017, producing 204 titles. TV shows and direct to video movies were eliminated, leaving 67 films. Synopses for the 67 films were reviewed using IMDb, the American Film Institute database and Wikipedia to determine if vaccines were featured in the film, leading to the elimination of 9 films. Ten films were unavailable for purchase, rent or interlibrary loan in the United States. The remaining 48 films were watched in their entirety. Three films did not feature a vaccine, leaving 45 for review. Films were assessed for their portrayal of both the scientific community and the vaccine, and were graded on a scale incorporating 10 variables to assess the realism of the vaccine portrayal. Tests of statistical significance used a Welch's t-test.

Summary of results The movies were released between the years of 1925 and 2016. Vaccines were portrayed negatively in 16 movies, with 14 of these released after 1990 ($p=0.0019$). The scientific community was portrayed negatively in 15 movies, with 14 of these released after 1990

($p=0.0002$). The mean realism score for films released prior to 1990 was 9.1 (0–10 scale) vs 7.3 for those released after 1990 ($p=0.0013$). Ten movies featured unrealistically severe adverse events after immunisation. All 10 were released after 1990 ($p=0.0029$). Ten movies featured conspiracy theories surrounding vaccines, with 8 of these films released after 1990 ($p=0.0816$).

Conclusions Cinematic portrayals of immunisation are increasingly unrealistic and negative. This trend appears to have begun in the 1990's, which corresponds to the onset of the modern anti-vaccination movement triggered by Andrew Wakefield's claim that the MMR vaccine caused autism. Whether the change in vaccine portrayal is reflective of societal beliefs or is influencing them should be the focus of future study.

368 THE FACTORS THAT IMPACT THE INITIATION AND COMPLETION OF THE HPV VACCINE AMONG HEALTH PROFESSIONAL STUDENTS

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10.1136/jim-2017-000663.368

Purpose of study The Human Papillomavirus (HPV) vaccine, can protect girls aged 9 through 26 from HPV strains most commonly linked to cervical, vaginal, and anal cancers or genital warts, as well as boys aged 9 through 15 from strains causing anal cancer or genital warts. While vaccination has proven to be effective in preventing disease caused by the common HPV types, the CDC has found that vaccination rates and coverage are still far below other vaccines given at that age range. This study aims to investigate the different factors that impact both the initiation and completion of the HPV vaccine series.

Methods used The survey was sent to health professional students at Western University of Health Sciences. The survey was divided into 3 parts with 45 questions in total: general identifying questions (age range, professional program, personal vaccination status, etc.), knowledge questions about HPV and vaccine, attitudes toward the HPV vaccine. Age information was grouped as 20–24, 25–29, 30–34, and >35 years of age. IRB approval was obtained on an exempt basis.

Summary of results 322 survey responses were analysed, 69.9% were women and 30.1% men. 162 women reported being vaccinated of which only 134 have completed the vaccine series. Most of the women reporting vaccination were 25–29 years old (101 respondents). There was a significant correlation between age range and HPV vaccine uptake ($p<0.0001$). However, knowledge acquired prior to or during graduate school did not correlate significantly with vaccination but did have a significant relationship with completion of the vaccination series ($p=0.0039$). Gender was not correlated with HPV knowledge acquired.

Conclusions This study suggests the importance of knowledge in the completion, not the initiation, of the HPV vaccine among health professional students. With the vaccine only recently becoming recommended to boys, it is worth considering ways to expand patient knowledge with the hopes of ultimately increasing the HPV vaccine completion rates and ultimately the effectiveness of the vaccine within both the male and female patient population.