Adolescent Medicine and General Pediatrics II
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

226 TWO ATYPICAL CASES OF PEDIATRIC LYMPHOHISTIOCYTOSIS

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10.1136/jim-2016-000365.226

Case Report Hemophagocytic Lymphohistiocytosis is often the top differential for pediatricians encountering an acutely sick child with lymphohistiocytosis. We present two cases in which lymphohistiocytoses were due to Rosai Dorfman and Systemic Lupus Erythematosis.

Case 1 is a 7 month old male with bilateral large cervical adenopathy who had failed a 5-day course of IV antibiotics. Parapharyngeal node biopsy revealed epithelioid histiocyte clusters and rare neutrophils in a background of granulomatous inflammation. Cultured tissue was positive for Serratia Marscesens, concerning for Chronic Granulomatous Disease. Open biopsy of an enlarged occipital node revealed marked sinus histiocytosis. Large eosinophilic histiocytes displayed emperipolesis of lymphocytes and granulocytes. Epithelioid histiocyte clusters were present, suggesting poorly formed granulomatous inflammation. These findings were consistent with a diagnosis of Rosai-Dorfman. Normal lab results for CGD and HLH were ultimately obtained.

Case 2 is a 17 year old male who presented with a 30 lb weight loss over 2 months, 3 weeks of daily fever, sore throat, cough, dizziness, progressive weakness, and syncope.

On exam he had post-cervical and axillary lymphadenopathy. Lymph node biopsy showed paracortical expansion with histiocytic cells. Lymphoid tissue displayed large geographic necrosis, karyorrhectic debris, and reactive histiocytes rimming necrotic areas. No neutrophils were seen. There were no pathogenic organisms. Interpretation was consistent with Kikuchi Disease, or histiocytic necrotizing lymphadenitis. Symptoms progressed, meeting 5 of 11 clinical criteria for the diagnosis of SLE, with oral ulcers, nonerosive arthritis, neurologic features, leukopenia <4000 on >2 occasions, and anti-Smith antibody. ANA was negative.

Pathological description of lymphadenopathy is essential in differentiating among varied histiocytic diseases. Pediatric lymphohistiocytic diseases have a broad differential diagnosis including lymphoma, HLH, CGD, Rosai Dorfmann, Kicuchi Syndrome and SLE. Accurate diagnosis of histiocytic lymphadenopathies is vital to appropriate treatment and prognosis of pediatric disorders.

227 SIGNIFICANT LOCAL PRACTICE VARIATION IN PREDNISONE DOSING FOR CHILDHOOD NEPHROTIC SYNDROME AFFECTS RELAPSING OUTCOMES

Roshan A, Catapang M, Sibley M, Matsell D, Mammen C. *BC Children's Hospital, Vancouver, BC, Canada.*

10.1136/jim-2016-000365.227

Purpose of Study Until recently, both pediatricians and pediatric nephrologists have cared for children with nephrotic syndrome (NS) across British Columbia (BC) without formal standardization of therapy including induction prednisone dosing for the initial episode of NS. We hypothesized that: 1) local historical practice variation in cumulative prednisone dosing was wide, and 2) those that were treated with lower doses of prednisone had worse relapsing outcomes based on prior literature.

Methods Used Retrospective cohort analysis of 139 NS cases from BC Children's Hospital (1990–2010). Exclusion criteria: secondary causes of NS, <1 year of age at diagnosis, and steroid resistance. We explored cumulative induction prednisone dose (mg/m^2) and defined a "low" prednisone dose group that was treated with less than the 1st quartile from our dosing distribution. Relapsing outcomes from the "low" dose group were compared to a group treated with higher doses including time to first relapse after completion of induction therapy (Kaplan-Meier, log-rank) and the proportion developing frequently relapsing NS (FRNS), defined as $\geq$4 relapses in any one year period over 2.5 years of follow-up (chi-square).

Summary of Results Cumulative prednisone dosing practice variation followed a wide distribution with median, 1st & 3rd quartile doses at 2450, 2000, & 3050 mg/m^2 respectively. Time to 1st relapse was significantly shorter in the "low" prednisone group ($\leq$2000 mg/m^2) compared to those treated with higher induction doses (p=0.002) with 50% of "low" prednisone patients relapsing at 8.5 wks after initial treatment vs 24.5 wks in those treated with higher doses. The proportion of those developing FRNS almost doubled with 23/38 (61%) from the "low" dose group compared to 32/101 (32%) treated with higher doses (p=0.003).

Conclusions Results from local historical data strongly justified our development of a clinical pathway for the treatment of childhood NS in order to standardize care across the province of BC. Goals of our clinical pathway include to significantly reduce practice variation, to minimize the number of undertreated patients with "low" prednisone dosing, and to improve upon relapsing outcomes. An audit of our clinical pathway is underway to determine if we have successfully achieved these goals.

228 THE CHILDHOOD NEPHROTIC SYNDROME CLINICAL PATHWAY REDUCES PRACTICE VARIATION AND IMPROVES RELAPSING OUTCOMES

Catapang M, Sanchez A, Roshan A, Sibley M, Humphreys R, Mammen C, Matsell D. *BC Children's Hospital, Vancouver, BC, Canada.*

10.1136/jim-2016-000365.228

Purpose of Study Nephrotic syndrome (NS) is a common pediatric kidney disorder. We have previously demonstrated considerable in-center practice variation in the prednisone treatment of these children at diagnosis. Under-treatment impacts on subsequent clinical course. In 2013 we initiated the Childhood Nephrotic Syndrome Clinical Pathway (CP) to address the needs of this population. We hypothesized that implementing this pathway would reduce variation in induction therapy and improve relapsing outcomes.

Methods Used Incident patients (IP) who met our definition of idiopathic NS and were diagnosed between Jan 2013–Jul 2016, followed at BC Children's Hospital (BCCH), and initiated on the CP were audited (n=24). Results were compared to a retrospective BCCH cohort that predated CP implementation (n=138). The cohorts were stratified based on whether they were intention to treat (ITT) or completed induction without relapse (C). Outcome variables included recommended and actual cumulative induction prednisone dosing (mg/m^2), total relapses per year, and time to first relapse.

Summary of Results A total of 24 IP (5±3.6 years old) with a mean follow-up of 444±254 days was compared to 138 historical controls (HC). There was a significant difference in the total cumulative induction prednisone dose between the IP-ITT and HC-ITT groups (3741±555 vs 2539±998 mg/m^2, p<0.001) with a marked decrease in the variation in dosing. The IP-ITT group achieved 96% of the CP recommended dose (3895±410 mg/m^2). There was also a significant reduction in the number of relapses at 2 year follow-up between the IP-ITT and HC-ITT groups (1.6±1.6 vs 3.5±3.1, p=0.01) and the IP-C and HC-C groups (0.8±1.1 vs 3.0±3.0, p=0.02). While the time to first relapse was longer in IP-C than HC-C, the difference lacked statistical significance (178 ±227 vs 135±200 days).

Conclusions The CP is an effective tool for the management of childhood NS. In our IP cohort it significantly reduced variation in induction prednisone dosing and impacted favorably on short-term relapsing outcomes. Results of this audit will be used to help guide prednisone dosing recommendations for future CP iterations.

229 FIDELITY TO THE CHILDHOOD NEPHROTIC SYNDROME CLINICAL PATHWAY: HOW WELL ARE WE DOING?

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10.1136/jim-2016-000365.229

Purpose of Study In 2013 the Childhood Nephrotic Syndrome Clinical Pathway (CP) was implemented at BC Children's Hospital (BCCH). Its goals are to standardize care, reduce practice variation, and improve the outcomes of children with nephrotic syndrome (NS) across British Columbia. To achieve this, the CP outlines various clinician- and patient-focused tasks vetted by our multidisciplinary Clinical Pathway Development (CPD) Team as important for best practice. The aim of this quality improvement study is to assess our local fidelity to CP recommendations.

Methods Used Incident patients diagnosed from Jan 2013-Jul 2016 were included (n=24). Core tasks to be completed during routine BCCH outpatient clinic visits and listed in the CP "Schedule of Ongoing Care," including dipstick teaching for home monitoring and sodium/fluid counselling for edema management, were reviewed. Our locally-developed "NS Clinic Worksheets" with embedded fidelity probes served as source documents for data abstraction. Fidelity was determined as the proportion (%) of completed tasks within the first 3 months post-diagnosis. Fidelity was further qualified on a scale of "very poor" (<20%), "poor" (20–40%), "moderate" (41–60%), "good" (61–80%), and "very good" (>80%).

Summary of Results Clinicians showed overall "good/very good" fidelity to CP recommendations for teaching families about prednisone (≥83%), urine dipsticks (≥80%), and sodium/fluid restriction (≥70%). "Moderate" fidelity was noted for calcium and vitamin D counselling (≤50%). Patients showed "very good" fidelity for taking prednisone as prescribed (≥83%) and "moderate" fidelity for completing their worksheets (a home monitoring tool for prednisone dosing and dipstick results; ≤42%) and bringing them to clinic for review (≤50%).

Conclusions Auditing fidelity and benchmarking performance is an easy but essential exercise in the CPD process. In spite of the variance seen across tasks, this audit enabled the identification of areas needing improvement and provided invaluable insight into the content validity of the current CP "Schedule of Ongoing Care." Results from this evaluation study will be used to guide adjustments to future CP iterations.

230 IDENTIFYING BIOMARKERS OF DISEASE PROGRESSION IN PEDIATRIC AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS

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10.1136/jim-2016-000365.230

Purpose of Study Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease and accounts for 5% of today's end stage renal disease population. Though children with ADPKD show normal renal function and creatinine clearance prior to adulthood, rapid cyst development is already occurring. In this study, we aimed to identify plasma biomarkers of disease progression in the pediatric ADPKD population.

Methods Used Plasma samples from 81 ADPKD patients aged 8–22 years were collected at baseline, whereas samples from a cohort of healthy children (60 subjects, aged 1–3 years) served as a control. Metabolomic analysis of plasma was performed using liquid chromatography-mass spectrometry and differences in biomarkers between the healthy subjects and ADPKD patients were evaluated. Metabolites with a P value<0.05 and an absolute fold change of 50% or greater were identified as significant. Pathway analysis was conducted on significant metabolites.

Summary of Results 117 metabolites were significantly changed between the ADPKD patients at baseline and the healthy children controls. Of these, 16 metabolites were decreased in the ADPKD cohort while 101 were increased. Of note, cardiovascular risk markers and intermediates of the methionine cycle (uric acid, allantoin, cysteine, S-adenosyl-homocysteine), intermediates of the Krebs cycle and glycolysis (pyruvate, α-ketoglutarate, D-glyceraldehyde-3-phosphate), and bile acids (deoxycholic and cholic acids) were increased in the ADPKD patients. An increase in renal insufficiency markers and tryptophan metabolites kynurenine and quinolinate was noted, with a decrease in kynurenine metabolite anthranilate. Hypoxanthine and nicotinamide were also decreased.

Conclusions We found several cardiovascular and renal risk markers to be increased in the pediatric ADPKD patients as compared to healthy subjects. Future work will involve targeted quantitation of the identified combinatorial markers as well as their translation into studies of disease progression.

231 PROTEINURIA, GLOMERULAR FILTRATION RATE AND ALLOGRAFT SURVIVAL IN PEDIATRIC POST RENAL TRANSPLANT POPULATIONS IN A SINGLE CENTER STUDY

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10.1136/jim-2016-000365.231

Purpose of Study Renal transplantation is the treatment of choice for pediatric patients with end-stage renal disease. Progressive decline of renal function is a general problem for pediatric patients after transplantation, with a 10 year graft survival of 55.6% (cohort year of 1994–2001). The purpose is aimed at identification of risk factors, such as disease recurrence, rejection, and chronic allograft nephropathy, that affect renal function may allow for a more rapid recognition and early intervention for patients at risk for early allograft loss. Estimated glomerular filtration rate (eGFR) and proteinuria have independently been associated with poor prognosis following renal transplantation (Amer, et al, Am J Transplant 2007). Association between these

two factors and graft survival has not been well-studied in pediatrics.

Methods Used A retrospective chart review was performed on 19 pediatric renal transplant patients in a unique, predominately Hispanic population followed at the University of New Mexico Children's Hospital who were transplanted between 2008–2013. Only kidney transplant patients younger than 18 years old at time of transplant, and patients with 1 month and 1 year post-transplant data, were included.

In addition to demographic data, eGFR (via Schwartz equation) and urine protein values were obtained at 6 month intervals for at least 1 year post-transplant. Percent graft loss over time was then compared and stratified by degree of proteinuria.

Summary of Results Kaplan-Meier analysis showed decreased graft survival in the proteinuria group, although not statistically significant due to small patient numbers. Additionally, the degree of proteinuria in our population varied significantly over time, making interpretation more difficult. However, patients with proteinuria did demonstrate a larger decline in eGFR over the follow up period than those without proteinuria.

Conclusions Degree of proteinuria likely impacts long term graft survival (as it does progression for chronic kidney disease), and the significance of the impact could be evaluated in a larger study.

232 EFFICACY OF STEROIDS IN PREVENTING LONG-TERM RENAL INVOLVEMENT IN PEDIATRIC PATIENTS WITH HENOCH SCHONLEIN PURPURA (HSP): A COMPREHENSIVE LITERATURE REVIEW

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10.1136/jim-2016-000365.232

Purpose of Study Patients with HSP are commonly treated with steroids; however, the effect of steroids on the long-term renal outcome remains unclear. The purpose of this study is to review the literature on the efficacy of early steroid treatment in preventing renal involvement in pediatric patients diagnosed with HSP.

Methods Used A literature review was conducted using PubMed and Google Scholar. Controlled studies published within the last 20 years which included pediatric patients 19 years of age and younger were included.

Summary of Results Six studies met our inclusion criteria (table below). All studies had patients who met the diagnostic criteria for HSP: purpura, abdominal pain, arthritis, and/or renal involvement. For the majority of the studies, patients were given prednisone or prednisolone 1–2 mg/kg per day for 1–2 weeks. Renal involvement was determined by a variety of methods including: protein and blood dipstick urine testing, microscopy, U-protein: U-erythrocytes ratios, urine protein: creatinine ratios, and/or blood tests. Interestingly, in two studies none of the patients had renal involvement initially but on follow-up 18 to 33% had renal involvement in both steroid and control groups. The studies reviewed did not find any effectiveness of steroids in reducing the risk of renal involvement except for one study (Kaku et al) that found steroids decrease the risk of long-term renal involvement.

Conclusions Our review demonstrated that steroids do not provide long-term advantage in preventing the development of HSP nephritis. The limitations included differing definitions of nephritis, different levels of HSP severity at presentation, small sample size and other confounding variables. Larger placebo controlled studies are needed to evaluate the long-term effectiveness of steroids in preventing long-term complications.

233 ACUTE KIDNEY INJURY IN 'ATYPICAL' KAWASAKI DISEASE

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10.1136/jim-2016-000365.233

Case Report: Introduction Sterile pyuria, trace proteinuria and nephromegaly are the common renal manifestations in Kawasaki disease (KD). We report acute kidney injury (AKI) presumed secondary to Acute Nephritic Syndrome

Abstract 232 Table 1

Author	Study Type	Age Range	N Control	N Treatment	N Initial Renal Involvement	Long Term Renal Involvement	Follow-Up
Bayrakci, 2007	Retrospective	3–19 years old	96	61	0	P=0.2 (18/96 control vs. 17/61 steroid)	3–60 months
Dudley, 2013	Placebo-Control	<18 years old	124	123	12 control, 26 steroid	P=0.33 (13/124 control vs. 18/123 steroid)	1 year
Huber, 2004	Placebo-Control	2–15 years old	19	21	2 control, 4 steroid	P=1.0 (2/19 control vs. 3/21 steroid)	1 year
Kaku, 1998	Retrospective	1.5–14.5 years old	115	79	0	P=0.46 univariate (39/115 control vs. 26/79 steroid) P=0.037 multivariate	1.0 to 76.1 months
Limpongsanurak, 2011	Prospective	2–15 years old	65	102	Not recorded	P=0.09	1 year
Ronkainen, 2006	Placebo-Control	<16 years old	87	84	16 control, 16 steroid	\"NS\" (36/87 control, 38/84 steroid)	6 months

(ANS) in 'atypical' KD.

Case A 6-year old previously healthy boy presented with 3 days of diffuse abdominal pain, vomiting, mucus diarrhea and fevers up to 103^0F. His physical exam revealed an irritable boy with diffuse abdominal pain, generalized tenderness of his extremities, a non-specific maculopapular rash over his chest, dried and cracked lips, and generalized edema. His initial laboratory studies revealed WBC 20,700 cells/mcL, Hb 10.8 gm/dl, platelet count 160,000 cells/mcL, elevated ESR 77 mm/hr and CRP 18.5 mg/dl and low serum albumin 2.5 g/dL. Ultrasound of the abdomen revealed nephromegaly (right 10.6 cm; left 11.5 cm; upper normal limit for age: 9.2 cm). Over the next 3 days he had intermittent fevers up to 101^0F and developed non-oliguric AKI with peak BUN of 46 mg/dl, creatinine of 3.7 mg/dl; FeNa of 20% and urinalysis revealing proteinuria, hematuria, and pyuria (urine protein: creatinine ratio: 6.3; RBC 61/hpf; WBC 82/hpf). Additional laboratory studies revealed low C3 (51 mg/dl) and C4 (10.4 mg/dl) levels, normal ASO titers, negative ANA, bacterial cultures and serology. His echocardiogram on day 5 revealed left anterior descending coronary artery dilation: 0.3 cm (z score: 2.6) with no tapering. He was treated with IVIG and planned renal biopsy was withheld. Soon thereafter, his clinical features improved, BUN and serum creatinine trended down to 11 mg/dl and 0.7 mg/dl respectively and urinalysis improved.

Discussion The term 'atypical' KD is reserved for patients who have atypical symptoms that are uncommon in classical KD, such as renal impairment and pleural effusion. ANS in KD that is characterized by hematuria, edema, hypertension, moderate proteinuria, mild AKI and hypocomplementemia as seen in our patient has been reported previously, but it is rare. Immune complex mediated mechanisms have been implicated in the pathogenesis of ANS in KD.

Conclusion Aggressive investigational work up for a febrile child with non-focal symptoms and AKI including echocardiogram and/or renal biopsy must be entertained to delineate the cause of renal injury.

Cardiovascular III
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

234 PROLIFERATION SIGNAL INHIBITOR (PSI) IN THE FIRST YEAR WITH INDUCTION THERAPY IS SAFE IN HEART TRANSPLANT PATIENTS

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10.1136/jim-2016-000365.234

Purpose of Study According to the FDA black box warning, everolimus should not be given in combination with anti-thymocyte globulin (ATG) induction therapy (which is given immediately after transplant). The large randomized trials with everolimus and cyclosporine (CsA) show an increased incidence of infection and infectious mortality when ATG induction was also given. It is believed that the combination of proliferation signal inhibitor (PSI: everolimus or sirolimus) and induction therapy along with calcineurin inhibitor (CNI: CsA or tacrolimus) therapy creates an over immunosuppressed state and a risk for infectious complication. It is not known if PSI started later, between 2–12 months after transplant, with ATG induction therapy is safe. Therefore, we sought to evaluate our patients started on PSI between 2–12 months in the first year to assess for safety.

Abstract 234 Table 1

Endpoints	Everolimus +ATG (n=27)	Everolimus+No Induction (n=15)	P-Value
Subsequent 1-Year Survival	100.0%	93.3%	0.197
Subsequent 1-Year Freedom from Any-Treated Rejection	88.1%	100.0%	0.173
Subsequent 1-Year Freedom from Treated Infection	80.2%	53.3%	0.128
Everolimus Initiation Time from Transplant, Mean Months±SD	6.5±2.5	6.3±2.8	0.869

Methods Used Between 2010 and 2014 we assessed 27 heart transplant (HTx) patients who were started on PSI between 2–12 months after transplant while being administered ATG induction at the time of transplant. These patients were compared to patients started on a PSI between 2–12 months but not given ATG induction therapy (n=15). Endpoints include subsequent 1-year survival, 1-year freedom from treated infection, and 1-year freedom from any-treated rejection.

Summary of Results Patients initiated on PSI in the first year post-transplant with induction therapy had similar outcomes and infectious complications compared to those patients maintained on PSI and CNI without induction therapy. Subsequent survival and freedom from rejection episodes were comparable in both groups.

Conclusions PSI in the first year (between 2–12 months) after transplant in HTx patients receiving ATG induction therapy appears to be safe and effective without increased risk for infectious mortality.

235 VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENTATION, RECOVERY VERSUS MORTALITY: A SYSTEMATIC REVIEW

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10.1136/jim-2016-000365.235

Purpose of Study For patients in cardiogenic shock, veno-arterial extracorporeal membrane oxygenation (VA ECMO) provides temporary circulatory support allowing time for recovery from a predominantly fatal state. However, patient survival rates and complications during and after VA ECMO use are still not well-defined due to

the absence of large randomized studies. This review was conducted to assess VA ECMO survival rates, both short and long-term, complication rates and primary causes of mortality within the published literature.

Methods Used A systematic search was conducted using PubMed, Google Scholar, American Heart Association and Trip database for use of VA ECMO in treating cardiogenic shock. Studies involving 10 or more patients and published in or after 2008 were included. Survival to thirty days, survival to hospital discharge or survival up to three years post ECMO were pooled from studies and analyzed. Prevalent complications that were evaluated included bleeding, renal failure, neurologic, sepsis/infection and lower extremity ischemia. Primary cause of mortality was assessed when available.

Summary of Results Twenty studies were included in the systematic literature review encompassing a total of 9,942 patients. The average weighted survival rate to hospital discharge from sixteen studies was 40.12%±7.37. Average survival to hospital discharge from patients who were successfully weaned from ECMO, as reported in three studies, was considerably higher at 79.76%±6.54%. Recovery was most common among acute, primary cardiac etiologies including myocardial infarction and fulminant myocarditis. The lowest one year survival rate following successful weaning was 78% and the highest one-year survival rate was 100%. Renal failure was the most common reported complication. Renal failure affected an average of 49.8% of patients. Multi-organ failure was the leading cause of death recorded.

Conclusions VA ECMO can rescue patients in cardiogenic shock secondary to primary cardiac etiologies, but still has low survival to hospital discharge. Acute etiologies have better long-term survival, but one-year survival remains relatively constant for both acute and chronic cardiac conditions. Randomized controlled studies with large sample sizes need to be conducted to fully assess the benefits, risks and effective weaning strategies for VA ECMO.

236 COMBINED HEART-KIDNEY TRANSPLANT VS HEART ALONE TRANSPLANT IN PATIENTS WITH TOTAL ARTIFICIAL HEART: IS IT VIABLE?

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10.1136/jim-2016-000365.236

Purpose of Study The total artificial heart (TAH) is a life saving device for patients (pts) with severe biventricular heart failure. TAH pts undergoing heart transplantation (HTx) are noted to have increased morbidity and mortality following HTx. This has been demonstrated in the Scientific Registry of Transplant Recipients (SRTR) database as well as United Network for Organ Sharing (UNOS) database. These pts may also have severe kidney disease which require combination heart-kidney transplant (HKTx). It is not known whether HKTx also increases morbidity and mortality post-Tx. We sought to answer this question by reviewing our experience in TAH implantation.

Methods Used Between 2013 and 2015 we identified 31 pts implanted with a TAH. We divided these pts into those that received combined HKTx and compared them to those with a heart alone. Endpoints included 1-yr survival, 1-yr freedom from cardiac allograft vasculopathy (CAV) defined as stenosis ≥30% by angiography, Non-Fatal Major Adverse Cardiac Events (NF-MACE: myocardial infarction, new congestive heart failure, percutaneous coronary intervention, implantable cardioverter defibrillator/pacemaker implant, stroke) and 1-yr freedom from any-treated rejection. Renal function was also assessed for both groups with serum creatinine and glomerular filtration rates (GFR) post-Tx and 1-yr freedom from hemodialysis.

Abstract 236 Table 1

Endpoints	TAH+HKTx (n=9)	TAH and HKTx Alone (n=23)	Log-Rank p-value
1-Year Survival	100.0%	84.4%	0.224
1-Year Freedom from CAV	100.0%	87.7%	0.207
1-Year Freedom from NF-MACE	88.9%	81.6%	0.633
1-Year Freedom from Any-Treated Rejection	88.9%	78.7%	0.574
1-Year Freedom from Dialysis	55.6%	80.4%	0.114
Pre-OHT GFR	17.8±6.8	68.2±24.5	<0.001
1-Month Post-Transplant GFR	92.8±23.0	82.4±40.2	0.592
6-Months Post-Transplant GFR	103.8±14.5	82.5±38.5	0.249

Summary of Results There was no statistically significant difference in 1-yr survival or 1-yr freedom from CAV, NF-MACE or any-treated rejection between the two groups. Renal function was improved in pts that received HKTx compared to those who received a heart alone. However, this was only prevalent in the first month, becoming similar at 6-mo post-Tx.

Conclusions Combined HKTx in pts with TAH appears to be reasonable as there does not appear to be an increase in morbidity or mortality.

237 SIDE EFFECTS OF PROLIFERATION SIGNAL INHIBITORS LIMIT THEIR PRACTICAL USE AFTER HEART TRANSPLANTATION

Arakawa LM, Aintablian T, Levine R, Hamilton M, Kobashigawa J. *Cedars-Sinai Medical Center, Los Angeles, CA.*

10.1136/jim-2016-000365.237

Purpose of Study Proliferation signal inhibitors (PSI) such as sirolimus and everolimus have been found in clinical trials to decrease rejection, decrease cardiac allograft vasculopathy and are associated with less cytomegalovirus infection. However, the side effect profile for these agents is high as demonstrated by discontinuation rates in the randomized clinical trials. The differences in side effects may offer greater insight to efficacy of PSI use. Therefore, we sought to identify the reasons for discontinuation of the PSIs at our single center.

Methods Used Between 2010 and 2014 we assessed 72 heart transplant patients who were placed on sirolimus or everolimus in the first year after transplant. Discontinuation rates and the reasons for discontinuation

Abstract 237 Table 1

Endpoints	First Year PSI Use (n=72)
Subsequent 1-Year Survival	97.1%
Subsequent 1-Year Freedom from Any-Treated Rejection	91.3%
Rejection During PSI Use	5.6% (4/72)
PSI Discontinuation	34.7% (25/72)
Reasons for Discontinuation	
Lower Extremity Edema	6.9% (5/72)
Renal Insufficiency	6.9% (5/72)*
Infection	6.9% (5/72)
Aphthous Ulceration	4.2% (3/72)*^
Rash	4.2% (3/72)^
Deep Vein Thrombosis	2.8% (2/72)
Leukopenia	1.4% (1/72)
Anemia	1.4% (1/72)
Other	2.8% (2/72)

*1 patient discontinued on everolimus due to renal insufficiency and aphthous ulceration
^1 patient discontinued on everolimus due to aphthous ulceration and rash development

were both noted. All patients had conditional 1-year survival. Complications post-transplant while on these drugs included infectious complications, renal insufficiency and rejection.

Summary of Results The PSIs as a group had a 34.7% (25/72) discontinuation rate, mostly due to lower extremity edema, infection, renal insufficiency, aphthous ulceration, rash. See table. When divided into everolimus vs sirolimus groups, the sirolimus group had more of these complications, yet this was not statistically significant.

Conclusions A relatively high PSI discontinuation rate (34.7%) in the first year after transplant limits the practical use of this group of medications.

238 TRENDS IN CARE OF PATENT DUCTUS ARTERIOSUS AMONG EXTREMELY PRETERM INFANTS IN THE UNITED STATES FROM 2003–2012

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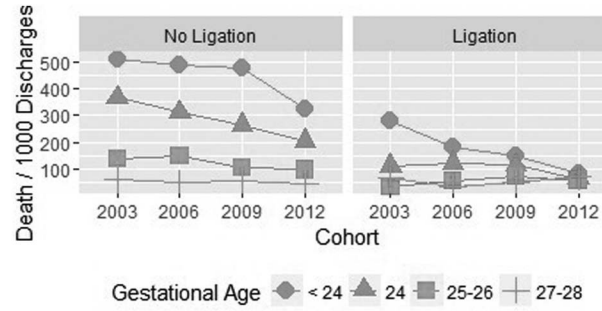
10.1136/jim-2016-000365.238

Purpose of Study There has been a significant controversy regarding treatment of patent ductus arteriosus (PDA) in preterm infants over the last decade. The impact of this controversy on rate of surgical ligation (SL), length of stay (LOS) and mortality is unclear.



Abstract 238 Figure 1

Methods Used Data from the national Health Care Cost and Utilization Project, Kids' Inpatient Database were abstracted for neonate s≤28 days old at admission with PDA using ICD-9-code 747.0 for 2003–2012. Patient were identified using ICD-9-code 765.21–24. SL was identified using ICD-9-code 38.85. Bivariate and analysis of variance was used to describe mortality and length of stay.

Summary of Results We identified 34,908 extremely preterm infants with a diagnosis of PDA from 2003–2012 with an overall mortality of 12%. SL has decreased significantly, with its peak at 26% in 2006 to 18% in 2012 ($p<0.001$) (Table). Overall median length of stay (IQR) has increased from 62 (24–85) days to 80 (53–105) days from 2003 to 2012 ($p<0.001$). Mortality among the 25–26 and 27–28 week gestational age (GA) have remained stable, however a significant decrease in mortality and increase in LOS among GA ≤24 weeks is observed (Figure).

Conclusions There have been an overall decrease in SL through time among extremely preterm neonates. Those who underwent SL had lower mortality than those who didn't, however both groups had an overall decrease in mortality through time. The decreased mortality and increased LOS among GA ≤24 weeks may be attributed to improved care among this high risk population.

239 THE RISK OF NAÏVE VS MEMORY PATIENTS AWAITING HEART TRANSPLANTATION: DOES IT MAKE A DIFFERENCE IN POST-TRANSPLANT OUTCOMES?

Krems JM, Aintablian T, Hamilton M, Kobashigawa J. *Cedars-Sinai Medical Center, Los Angeles, CA.*

10.1136/jim-2016-000365.239

Purpose of Study Sensitized patients (pts) awaiting heart transplantation (HTx) are known to have less optimal post-transplant outcome. Those pts. at risk for sensitization include previous blood transfusions, pregnancy, and/or

Abstract 238 Table 1

	Total	2003	2006	2009	2012	p
n	34,908	4,805	6,619	10,706	12,777	
Mortality (%)	4,041 (12)	653 (14)	814 (12)	1,270 (12)	1,303 (10)	<0.001
LOS (median[IQR])	70 [37,95]	62 [24,85]	60 [21,81]	70 [35,93]	80 [53,105]	<0.001
Surgical Ligation (%)	7,651 (22)	1,113 (23)	1,710 (26)	2,499 (23)	2,328 (18)	<0.001

Abstract 239 Table 1

Endpoints	Naïve (n=68)	Memory/No Abs (n=84)	Memory w/ Abs (n=63)	Log-Rank P-Value
2-Year Freedom from de novo DSA	92.2%	83.2%*	71.0%**	0.012
2-Year Survival	88.9%	85.4%	89.4%	0.637
2-Year Freedom from NF-MACE	87.8%	88.4%	92.8%	0.591
1-Year Freedom from Any-Treated Rejection	82.3%	82.9%	87.9%	0.657

*p=0.093 compared to Naïve category patients
**p<0.05 in comparison to Naïve category patients

organ transplants. We sought to evaluate our pre-HTx pts., dividing them into naïve (pts. without sensitization) vs memory (pts. at risk for sensitization or with detected circulating antibodies) and comparing them for post-transplant outcomes.

Methods Used Between 2010 and 2013 we assessed 215 patients awaiting HTx and divided them into memory vs naïve groups. Patients in the memory category were further divided into those who did and did not have detectable circulating anti-human leukocyte antigen (HLA) antibodies. Outcomes included 2-year development of *de novo* donor specific antibodies (DSA), first-year rejection including cellular or antibody-mediated rejection, 2-year survival and 2-year freedom from Non-Fatal Major Adverse Cardiac Events (NF-MACE: myocardial infarction, new congestive heart failure, percutaneous coronary intervention, implantable cardioverter defibrillator/pacemaker implant, stroke).

Summary of Results The memory sub-group with detectable pre-HTx anti-HLA antibodies was found to have significantly reduced 2-year freedom from *de novo* DSA development. There also appeared to be a numerical trend for reduced 2-year freedom *de novo* DSA development in the memory subgroup without detectable pre-transplant anti-HLA antibodies compared to the naïve group (p=0.093). There was no difference in 2-year survival, 2-year freedom from NF-MACE and 1-year freedom from any-treated rejection in all three groups.

Conclusions Patients awaiting HTx who have memory paired with pre-transplant anti-HLA antibodies appear to be at greater risk for the development of de novo DSA. These patients should be considered for anti-humoral immunosuppression therapy at the start of HTx to prevent these complications.

240 AORTIC DISSECTIONS AND STIMULANT DRUG ABUSE IN NEW MEXICO: A 39-YEAR RETROSPECTIVE REVIEW

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10.1136/jim-2016-000365.240

Purpose of Study Acute aortic dissection is a potentially catastrophic medical emergency with high rates of mortality. Untreated mortality approaches 33% within the first 24 hours, and 50% within 48 hours. Aortic dissection creates a split in the aortic media, allowing blood to enter and create a second lumen. Fixed sites of the vessel pose an increased risk for dissection due to greater impact of shear stress by pulse pressure. Methamphetamine and cocaine predispose to dissection via a catecholamine surge that raises shear stress and propagates intimal tears. The purpose of this study is to identify and characterize deaths due to aortic dissections in a culturally diverse autopsy population with a focus on illicit stimulant drug cases.

Methods Used We retrospectively reviewed electronic autopsy records at a statewide medical examiner's office. Autopsy cases were identified by searching death certificates in the database for "aortic dissection."

Summary of Results In a 39-year period (1977–2016) in New Mexico, 220 aortic dissection deaths were autopsied. Decedents were predominantly male (66%), White non-Hispanic (67%), and 18 to 96 years of age. Toxicology was tested in 64% of cases and identified stimulant-related deaths (7.7%). 42% of stimulant-related deaths lacked history or scene findings suspicious for drug use. The most common risk factor for dissection was hypertension (53.6%). 23% of decedents were seen within two weeks by a physician prior to being found dead.

Conclusions Several decedents with stimulant drug-related dissections lacked history or scene findings that may prompt a pathologist to test for illicit drugs. This highlights the need for stimulant toxicology testing on all aortic dissection cases given that a positive stimulant-related dissection would change the manner to accident.

Aortic dissection was missed in 24% of decedents seen by a physician within two weeks of death. This emphasizes the importance of autopsy to allow for appropriate classification of manner of death and provides feedback to clinicians to improve understanding and diagnosis of aortic dissection.

241 DOES SOCIOECONOMIC STATUS IMPACT OUTCOME FOLLOWING MECHANICAL CIRCULATORY SUPPORT DEVICE IMPLANTATION?

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10.1136/jim-2016-000365.241

Purpose of Study Although the use of mechanical circulatory support devices (MCSD) has been increasing over the past 5 years, complications rates have been prevalent and have not decreased over this period of time. There is concern that compliance with medications and care of the device affects post-implant complication rates may be related to socioeconomic status (SES). Lower SES has been associated with poor medical compliance in other diseases. We sought to assess whether lower SES is truly associated with poor outcome after MCSD implantations.

Methods Used Between 2010 and 2015 we evaluated 209 patients (pts) who received an MCSD. Insurance status at the time of heart transplantation was used as a surrogate

Abstract 241 Table 1

Endpoints	Private Insurance (n=157)	Medicare+Supplemental Insurance (n=15)	Medicare Alone (n=25)	Medicaid (n=12)	P-Value
6-Month Survival	77.2%	55.6%	78.9%	66.7%	0.331
6-Month Freedom from Stroke	78.5%	80.0%	91.7%	62.3%	0.436
6-Month Freedom from Infection	42.9%	25.7%	45.7%	59.7%	0.585
6-Month Freedom from GI Bleed	80.6%	82.5%	80.0%	88.9%	0.969
6-Month Freedom from Pump Thrombosis	93.8%	100.0%	100.0%	88.9%	0.445
6-Month Freedom from Device Malfunction	78.6%	100.0%	94.4%	66.7%*	0.219
Transplantation within 6-Months Post-MCS Implantation (%)	31.2% (49/157)	13.3% (2/15)	52.0% (13/25)**	16.7% (2/12)	0.206

*p=0.080 compared to Medicare+supplemental insurance group
**p<0.05 compared to Medicare+supplemental insurance group

for SES: private, Medicare+supplemental insurance, Medicare alone and Medicaid. By financial criteria, Medicaid pts were viewed as the lower SES group. 6-month complications after surgery were assessed, including development of pump thrombosis, stroke, infection, GI bleed, and device malfunction (characterized by MCSD system ceasing to operate at intended design specifications and/or performance). 6-month survival and/or transplantation were also included.

Summary of Results Medicaid pts, who comprised 5.7% of the total MCSD population, had a numerical trend towards reduced freedom from device malfunction compared to the patients with Medicare+supplemental insurance (p=0.080). There was no significant difference associated with 6-month survival or 6-month freedom from stroke, infection, GI bleed and pump thrombosis.

Conclusions Lower SES appears to be associated with a higher prevalence of MCSD malfunction. These pts may require closer supervision in order to maintain compliance and avoid complications. Further investigation with a larger population size is warranted.

Endocrinology and Metabolism II
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

242 YOUTH WITH TYPE 1 DIABETES HAVE HEPATIC AND PERIPHERAL INSULIN RESISTANCE

Stuppy JJ,[1,2] Green M,[1,2,3] Bergman B,[4] Coe G,[1] Baumgartner A,[1] Bacon S,[4] Sherzinger A,[5] Pyle L,[6,7] Nadeau KJ[1,3]. *[1]UCAMC, Aurora, CO; [2]UCAMC, Aurora, CO; [3]UCAMC, Aurora, CO; [4]UCAMC, Aurora, CO; [5]UCAMC, Aurora, CO; [6]UCAMC, Aurora, CO; [7]Colorado School of Public Health, Aurora, CO.*

10.1136/jim-2016-000365.242

Purpose of Study Youth with type 1 diabetes (T1D) often have difficulty obtaining optimal glucose control which may relate to insulin resistance (IR). We sought to assess hepatic and peripheral IR in youth with and without T1D.

Methods Used Insulin action was measured by a three-phase hyperinsulinemic-euglycemic clamp (basal, 16 and 80 mU/m^2/min) in 77 subjects (36 with T1D). Volunteers were mostly normal weight, more females than males, roughly 15 years of age and 90% were sedentary. T1D youth had an A1C 8.5±1.4% and had had T1D for 51 months.

Summary of Results Youth with T1D had significant peripheral IR compared with controls as evidenced by a lower glucose infusion rate 10.0±4.1 (mg/kgfat free mass/min) vs. 16.5±4.8, mean±STDev; P<0.001 and metabolic clearance rate 7.7±3.2 (ml/kg/min) vs. 10.1±3.8; P<0.008. Endogenous glucose release was higher in T1D 2.5±2.4 (mg/kg/min) vs. 1.1±0.75; P<0.003. However, youth with T1D had less hepatic fat (P<0.02), visceral fat (P<0.01), and lower markers of hepatic inflammation (P<0.008).

Conclusions Youth with T1D have higher multi-organ IR compared to youth without diabetes despite better traditional markers of metabolic syndrome relative to control youth. Furthermore, the mechanism is not similar to the mechanism seen in T2D. Youth with T1D may benefit from medication that improves insulin sensitivity.

243 THE EFFECT OF OBESITY ON INSULIN RESISTANCE AND CARDIOVASCULAR RISK IN TYPE 1 DIABETES

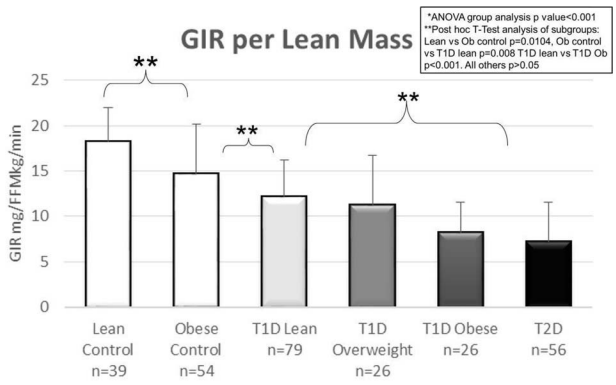
Strickland K,[1] Green M,[2] Bjornstad P,[2] Truong U,[2] Pyle L,[2] Baumgartner A,[2] Coe G,[2] Thurston J,[2] Reusch JE,[2] Nadeau KJ[2]. *[1]University of Oklahoma, Oklahoma City, OK; [2]University of Colorado-Anschutz Medical Campus, Aurora, CO.*

10.1136/jim-2016-000365.243

Purpose of Study In a cross sectional study of 131 youth with type 1 diabetes (T1D) (median [25–75]: 16 [14, 17] years of age, Tanner 5 [4, 5])—we analyzed the impact of obesity on cardiovascular (CV) health and insulin resistance. This cohort was compared to healthy controls and a cohort with type 2 diabetes (T2D) to assess where on a spectrum T1D patients compare regarding IR. We hypothesized that obesity would worsen CV health and IR.

Methods Used The T1D cohort was broken into categories based on BMI percentile (lean [n=79], overweight [n=26], and obese [n=26]). The T1D cohort was matched to lean control [n=59], obese control [n=54], and T2D cohorts [n=56]. All subjects underwent fasting labs and a hyperinsulinemic euglycemic clamp to evaluate insulin sensitivity (GIR). CV measures included echocardiography, exercise testing, and brachial artery distensibility (vascular stiffness). T1D subcohorts were compared by ANOVA.

Summary of Results Glucose infusion rate (GIR) per free



Abstract 243 Figure 1

fat mass was significantly lower in the T1D cohorts (19.29 [14.40, 21.30] in lean control vs 12.35 [9.44, 14.78] in lean T1D p<0.001). In addition, obesity worsened GIR per FFM in T1D (12.35 [9.44, 14.78] in lean vs 7.74 [5.67, 10.66] in obese, p<0.001). While systolic function did not vary among the T1D groups, diastolic function (mitral E/A, septal E:E', and lateral E:E') showed worsening with obesity. VO_2 Max was markedly decreased with obesity in T1D, as was BrachD.

Conclusions Obesity paints a negative cardiovascular picture for T1D adolescents. Therefore, more research is needed on obesity in T1D as well as a heightened clinical focus on managing weight in T1D to prevent future CVD.

244 THE RELATIONSHIP BETWEEN ACTIGRAPHY AND CONTINUOUS GLUCOSE MONITORING IN YOUTH WITH CYSTIC FIBROSIS

Branscomb R, Vigers T, Campbell K, Pyle L, Nadeau KJ, Simon S, Chan C. *University of CO School of Medicine, Aurora, CO.*

10.1136/jim-2016-000365.244

Purpose of Study Disrupted sleep is associated with worse insulin sensitivity (IS) and diabetes control in type 1 and type 2 diabetes. CF youth have decreased sleep quality and abnormal glycemia compared to healthy youth, but the association between sleep and glycemia in CF has not been well studied. We examined the association between actigraphy and glycemia, as measured by continuous glucose monitoring (CGM) and fasting estimates of IS, in CF youth.

Methods Used 43 youth with CF (13.8±2.7 years) and 13 healthy controls (HC) (15.2±4.6 years) wore an Actiwatch for 7 days along with CGM. CF youth were classified as normal glucose tolerant (NGT), abnormal glycemia (AGT), or CF-related diabetes (CFRD) by oral glucose tolerance testing (OGTT). Two-sample independent t-tests tested the association between actigraphy and CGM outcomes in CF vs controls. Spearman's coefficients tested correlations between actigraphy and CGM outcomes as well as IS estimates in the CF cohort. Significance was set at 0.05.

Summary of Results CF youth had greater sleep onset latency (16±12 vs 9±6 min, p=0.01), wake after sleep onset (WASO) (71±39 vs 49±25, p=0.02), and lower sleep efficiency (83%±7 vs 87%±5, p=0.02) compared to HC. CF youth had higher average glucose, standard deviation, peak glucose, time >140 and >200 mg/dL, and <60 mg/dL on CGM compared to HC (p<0.05). In CF patients, higher day minimum glucose correlated negatively with total sleep time and sleep efficiency. There were no significant correlations between IS estimates and actigraphy in the overall CF cohort. However, by subgroup, 1/c-peptide correlated with longer sleep time in AGT (r=0.5, p=0.02), and with onset latency (r=-0.6, p=0.03), sleep efficiency (r=0.6, p=0.05), and WASO (r=-0.7, p=0.01) in CFRD.

Conclusions CF youth had more disrupted sleep than HC as shown by greater onset latency and WASO, and lower sleep efficiency. Associations between higher minimum sensor glucoses and decreased sleep time and efficiency were noted. In CF youth with dysglycemia, better IS, reflected by greater 1/c-peptide, correlated with greater sleep time and efficiency, shorter onset latency, and fewer WASO. Future studies are needed to investigate the directionality and mechanisms behind the sleep and glycemia/IS relationship in CF.

245 AN ASSESSMENT OF DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS

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10.1136/jim-2016-000365.245

Purpose of Study American Diabetes Association (ADA) diagnostic criteria for diabetic ketoacidosis (DKA) include the triad of ketonuria, hyperglycemia (glucose ≥250 mg/dl) and a serum bicarbonate (HCO_3^-) ≤18 meq/l. However, serum HCO_3^- is not specific for DKA, and ADA recommendations on laboratory testing for diabetes state that urine ketone testing should not be used for diagnosing DKA because of its qualitative nature and its inability to detect the dominant ketone body anion in DKA, beta-hydroxybutyrate (βOHB). Because of these limitations, we previously suggested that an admission serum βOHB ≥3.8 mmol/l could be used in place of these criteria to diagnose DKA.

Methods Used In the present study, we reviewed records from adult DKA admissions for the years 2012–2016 to assess the sensitivity and specificity of the ADA criteria, using βOHB ≥3.8 mmol/l to define DKA. Trace or negative ketonuria was considered to be inconsistent with a DKA diagnosis, whereas small, moderate or large ketones were considered to be consistent with DKA. Records were reviewed on 224 people with DKA and 151 individuals with diabetes but not DKA (βOHB<3.8).

Summary of Results Among DKA patients, HCO_3^- was >18 meq/l in 17%, consistent with previous reports. Urine ketones were negative to trace in 21%, and glucose was <250 mg/dl in 4%. Urine ketones and HCO_3^- were both negative for DKA in 7%. Among individuals who did not have DKA, 17% had small to large urine ketones, 18% had a HCO_3^- ≤18 meq/l, and 4% had both. Thus, 35% of patients who had DKA as defined by βOHB lacked one or more of the ADA diagnostic laboratory criteria, and 31%

who did not have DKA fulfilled the criteria for DKA with respect to HCO_3^-, ketonuria, or both.

Conclusions When patients with diabetes who are admitted to the hospital are characterized as having DKA or not having DKA based on the admission serum βOHB, there is substantial discordance with ADA diagnostic criteria. Specifically, HCO_3^- and urine ketones were often at odds with the βOHB results. This is not surprising, considering the limitations of the urine ketone test and the fact that a serum HCO_3^- ≤18 meq/l is not specific for DKA. These results argue in favor of the use of serum βOHB for the purpose of diagnosing DKA, at least in hospitals that have sufficient DKA admissions to justify test availability.

246 RELATIONSHIPS BETWEEN BODY FAT DEPOTS AND INSULIN SENSITIVITY IN PEOPLE WITH AND WITHOUT TYPE 2 DIABETES

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10.1136/jim-2016-000365.246

Purpose of Study Obesity is defined by the World Health Organization as a body mass index (BMI) ≥30 kg/m^2. However, the occurrence of metabolic complications (e.g., hypertension, dyslipidemia) in obese individuals is highly variable, and numerous studies have shown a relatively weak relationship (R^2=0.1–0.2) between BMI and insulin sensitivity. It has been suggested that this is due to differences in body fat distribution. The contribution of liver versus muscle to systemic insulin resistance has also been reported to be variable.

Methods Used In the present study, we enrolled overweight and obese individuals with (DM, n=13) and without (ND, n=16) type 2 diabetes. We measured insulin sensitivity with a 2-h oral glucose tolerance test, calculating the insulin sensitivity index (ISI) according to Matsuda. We also quantified regional adipose tissue depots (leg fat [LF], visceral fat [VF] and trunk fat [TF]) and total body fat (TBF) using the combination of dual energy X-ray absorptiometry and single-slice (L2-L3) abdominal CT scans.

Summary of Results There was no difference between DM and ND in age (52±2 v 47±3 y), BMI (34±1 v 32 ±1 kg/m^2), TBF (40±2 v 40±3 kg), TF (25±1 v 23 ±1 kg), or LF (10±1 v 11±1 kg), all p=NS. However, the DM group had greater VF (328±18 v 230±22 cm^3, p<0.005) and borderline lower ISI (2.0±0.3 v 2.9±0.3, p=0.06). In DM, ISI did not correlate with TBF, TF or VF, but there was a borderline correlation between ISI and LF (R=0.53, p=0.06) and a strong negative correlation between ISI and the VF:LF ratio (R=-0.75, p=0.003). In ND, there was no correlation between ISI and VF, LF or VF/LF ratio, but a negative correlation between ISI and both TF (R=-0.64, p<0.01) and TBF (R=-0.51, p=0.04).

Conclusions These results indicate that in DM, lower body fat is positively associated with insulin sensitivity, and that the relative size of the VF depot in relation to lower body fat may be an important predictor of insulin resistance. In contrast, in ND individuals it appears that subcutaneous fat (but not VF) is most closely associated with insulin resistance. These differences may be due to differences in the regulation of regional lipolysis between groups. Whether these findings relate to discordance between hepatic and skeletal muscle insulin sensitivity will require further investigation.

247 INSULIN RESISTANCE, RELATIVE POSTPRANDIAL HYPERINSULINEMIA AND MITOCHONDRIAL DYSFUNCTION IN NORMAL WEIGHT GIRLS WITH PCOS

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10.1136/jim-2016-000365.247

Purpose of Study Girls with polycystic ovarian syndrome (PCOS) have an increased risk of developing diabetes, which may relate to altered glucose and fat metabolism. Obese girls with PCOS have increased liver fat, decreased insulin sensitivity (IS) and muscle mitochondrial dysfunction, but studies of these measures in normal weight girls with PCOS are lacking. The study's purpose was to assess IS, mitochondrial function and hepatic fat in normal weight girls with and without PCOS.

Methods Used Normol-glycemic normal weight adolescents, 18 with PCOS (PCOS; age 15.9±1.8 years) and 20 without PCOS (normal weight control (NWC); age 15.0 ±2.1 years) were studied. IS was assessed with a hyperinsulinemic-euglycemic clamp and a 2 hour oral glucose tolerance test. Hepatic fat and visceral fat were determined via MRI. Fasting biochemical measurements were also obtained. Post-exercise muscle mitochondrial function was assessed with ^{31}Phosphorus MR spectroscopy and presented as the oxidative phosphorylation rate; ADP and Phosphocreatine time constants.

Summary of Results Both groups had similar demographics and physical attributes including age, body mass index, menarche, % total body fat, waist/hip ratio, % visceral fat, daily activity and diet. NWC and PCOS had similar fasting labs with the exception of elevations of total testosterone, DHEAS and anti-mullerian hormone in PCOS, as expected. PCOS had a significantly higher % liver fat compared to NWC (1.1 (0.6, 1.9%) vs. 0.0 (0.0,0.7); p=0.017). Clamp assessed IS was lower in PCOS (16.0(5.8, 19.3) mg/kg fat free mas/min vs. 20.2 (17.2,22.1); p<0.025). Insulin and glucose concentrations 2 hours after oral glucose were higher in PCOS (114 IU/mL ±26 vs. 42±25; p=<0.001 insulin; and glucose 119±22 mg/dl vs. 85 ±23; p=0.011). Rates of muscle oxidative phosphorylation were slower (P=0.004) and ADP (P=0.018) and PCR (P=0.018) time constants longer in PCOS.

Conclusions In addition to the evidence for relative postprandial hyperinsulinemina, normal weight girls with PCOS have significantly decreased IS and mitochondrial function, and increased hepatic fat compared to NWC with regular menses.

Gastroenterology Concurrent Session 8:00 AM – 10:00 AM Friday, January 27, 2017

248 EVALUATE AN ANTI-REFLUX PROGRAM IN TREATING LARYNGOPHARYNGEAL REFLUX SYMPTOMS COMPARED WITH ANTI-REFLUX MEDICATIONS

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10.1136/jim-2016-000365.248

Purpose of Study Laryngopharyngeal reflux (LPR) causes chronic cough, hoarseness, dysphonia, dysphagia, globus, constant throat clearing and a multitude of other extraesophageal maladies. Though anti-reflux medications have been used to treat LPR for the past 20 years, concerns over their effectiveness and associated short and long-term adverse effects have called into question their widespread application. We employed an anti-reflux program including a two-week diet, alkaline water, and medication to determine whether the combination could relieve symptoms better than medication alone.

Methods Used A database was built by reviewing patients treated for LPR at the Loma Linda Voice and Swallow Center. Patients were included in the study group if they completed an anti-reflux program consisting of a two-week induction diet, alkaline water, behavioral modifications, and anti-reflux medications (PPI and H_2 blocker). Patients were included in the control group if they completed anti-reflux medications and behavioral modifications only. All patients were asked to complete VHI-10, RSI, CSI, DSI and EAT-10 surveys and underwent laryngoscopy for examination and RFS scoring.

Summary of Results Of 105 patients in the study group (mean age: 60, mean BMI: 29), 97 (92%) patients reported subjective improvement in their LPR symptoms after an average 32-day follow-up. There were significant differences in RFS, RSI, and CSI scores ($p<0.01$) before and after the anti-reflex program. No significant differences were found in VHI, DSI, and EAT-10 scores ($p>0.01$). Of 38 patients presenting with a chief complaint of cough, 37 patients reported subjective improvement with a significant CSI score improvement from 12.3 to 8.2 ($p=0.0005$). Among 81 controls (mean age: 59, mean BMI: 29), 39 (48%) patients reported subjective improvement in their LPR symptoms after an average 62-day follow-up. No significant differences were found in RFS, RSI, CSI, VHI, DSI, or EAT-10 scores.

Conclusions The anti-reflux program is a powerful tool for treating motivated patients with LPR symptoms. This program yielded better results than medical treatment alone. With a goal of reducing risks associated with medical therapy, further studies should examine the success of dietary control alone for LPR.

249 CANCELLED

250 SMALL MOLECULE INHIBITION OF THE CHEMOKINE RECEPTOR CXCR3 ATTENUATES EXPERIMENTAL CROHN'S DISEASE

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10.1136/jim-2016-000365.250

Purpose of Study Inflammatory bowel diseases (IBD; namely Crohn's disease and Ulcerative colitis) are a group of disorders characterized by idiopathic chronic inflammation of the intestine. While IBD affects over 1.6 million patients in the US there is currently limited treatment options and no cure. Pathogenic $CD4^+$ T cell subsets are central to the pathogenesis of IBD and perpetuate the chronic inflammation observed. Thus understanding the molecular regulation of T cell subsets within the inflamed intestine is central to developing novel therapeutic modalities. Previous work has implicated the chemokine receptor CXCR3 in trafficking pathogenic T cells into inflamed tissues but its role in IBD is not well characterized. Our work aimed to define the expression profile of CXCR3 and its ligands (CXCL9, CXCL10, and CXCL11) and assess whether therapeutic blockade of CXCR3 can attenuate experimental Crohn's disease.

Methods Used TNF-transgenic mice ($TNF^{\Delta ARE/+}$) that develop a Crohn's disease-like ileitis or WT counterparts received once daily subcutaneous injections of the small molecular inhibitor AM487 (10 mg/kg) for 10 days. PCR, flow cytometry, ELISA, FACs sorting, and histopathology were used to evaluate the expression profile of CXCR3 and its ligands, the cytokine phenotype of $CXCR3^+$ leukocytes, and the extent of disease.

Summary of Results CXCR3 is expressed preferentially by effector memory (T_{EM}) $CD4^+$ and $CD8^+$ T cells in the gut and in addition to its ligands, is significantly increased during active disease. Treatment of TNF-transgenic mice with the small molecule CXCR3 inhibitor, AM487 reduced effector $CD4^+$ and $CD8^+$ T cell infiltrates, inflammatory cytokine production and attenuated all histological indices of ileitis compared to vehicle-treated counterparts.

Conclusions $CXCR3^+$ T cells play an important role in potentiating inflammation during experimental Crohn's disease and our data identifies the blockade of CXCR3 as a potential therapeutic target.

251 THE EFFECTIVENESS OF PROBIOTICS IN TREATING PEDIATRIC FUNCTIONAL ABDOMINAL PAIN

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10.1136/jim-2016-000365.251

Purpose of Study Although probiotics are commonly used as a treatment modality for adult gastrointestinal disorders, their efficacy in the pediatric population remains controversial. The purpose of this study is to review the literature

Abstract 251 Table 1

Reference	Treatment (n)	Control (n)	Diagnostic Criteria	Age	Duration of Supplementation	Follow-up Period	P-value	
							Frequency	Intensity
Weizman (2016)	47	46	Rome III	6–15 years	4 weeks	4 weeks	<0.02	<0.01
Eftekhari (2015)	40	40	Rome III	4–16 years	8 weeks	none	0.16	0.16
Romano (2010)	30	26	Rome III	6–16 years	4 weeks	4 weeks	<0.05	<0.001
Francavilla (2010)	FAP: 25 IBS: 42	FAP: 31 IBS: 38	Rome II	5–14 years 0.001	8 weeks	8 weeks	0.6 0.001	0.05
Gawronska (2007)	FAP: 24 IBS: 18	FAP: 23 IBS: 19	Rome III	6–16 years	4 weeks	none	0.93 0.02	0.57 0.1

on the effectiveness of probiotics in the treatment of functional abdominal pain (FAP) in pediatric patients.

Methods Used A systemic literature review was conducted through online databases such as Google Scholar, PubMed, and Cochrane. Only controlled studies with pediatric patients under 18 years of age who fulfilled the Rome II or III diagnostic criteria for FAP were included for analysis.

Summary of Results We analyzed 5 studies that met our inclusion criteria (see Table 1). Each study measured the effects of probiotic Lactobacillus rhamnosus strain GG or Lactobacillus reuteri DSM 17938. Duration of supplementation ranged from 4–8 weeks with a 0–8 week follow-up period. A majority of studies demonstrated statistical significance in the effectiveness of Lactobacillus in reducing perceived frequency and/or intensity of FAP. In one study (Eftekhari), there was no difference between the Lactobacillus and the placebo groups; however, both Lactobacillus and placebo decreased the frequency and intensity of abdominal pain significantly ($p=0.0001$), pointing towards the psychological component of FAP. Two studies (Francavilla and Gawronska) included both FAP and irritable bowel syndrome (IBS) patients. Both of these studies demonstrated effectiveness in treating IBS, but only one of the two studies showed improved intensity of FAP.

Conclusions Majority of studies suggest that probiotics are effective in relieving frequency and/or intensity of pediatric FAP; however, larger placebo controlled trials focused on optimal strain, dose, treatment duration, and longer follow-up periods are necessary to confirm their efficacy in the pediatric population.

252 HEPATITIS C RELATED NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA: IDENTIFYING GENETIC RISK FACTORS

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10.1136/jim-2016-000365.252

Purpose of Study Hepatitis C (HCV) is the leading cause of Hepatocellular Carcinoma (HCC) in the United States and worldwide, accounting for an estimated 50% of cases. Classically HCV has been thought to contribute to oncogenesis via inflammation and the subsequent liver cirrhosis; however recent evidence indicates that HCV also plays a role in direct oncogenesis in a subset of patients. This study seeks to investigate whether a genetic etiology for HCV-related non-cirrhotic HCC can be identified within this patient population.

Methods Used Exome sequencing was conducted upon tumor and healthy liver samples from 9 patients with HCV-related non-cirrhotic HCC. All samples were previously confirmed to be negative for aflatoxin exposure and Hepatitis B coinfection, and the prevalence and deleterious nature of genetic variants were assessed using known allele frequencies and CADD scores respectively.

Summary of Results Somatic tumor sequencing in the 9 patient samples revealed no abnormal or shared gene pathway mutations. Germline sequencing, however, identified several shared mutations that were predicted to be pathogenic, all notably within the TAP1 – ERAP1/ERAP2 pathway responsible for antigen presentation. Altogether 6 of the 9 germline samples contained significant, heterozygous mutations within the pathway, with 4 of the 9 patients demonstrating one or more mutations within the ERAP2 gene alone. Based upon known allele frequencies, the probability of attaining the observed constellation of mutations due to random chance was calculated to be <0.001.

Conclusions TAP1 and ERAP1/ERAP2 are responsible for cleaving and trimming foreign peptides into the length suitable for HLA presentation and subsequent immune recognition. The mechanism by which HCV mediates direct oncogenesis remains unclear, but it is plausible that altered antigen presentation could exacerbate this process by affecting immune response and viral loads. As further study focused gene sequencing will be performed on additional HCV-related non-cirrhotic HCC samples, and all samples will undergo genomic HLA-typing to fully investigate the role of the antigen presentation pathway. If identified the results could have implications for HCC screening in HCV patients, with a potential outcome of altering HCC screening guidelines to emphasize earlier or cirrhosis-independent screening.

253 EFFICACY OF ANTACIDS IN TREATING GASTROESOPHAGEAL REFLUX (GERD) IN INFANTS: A LITERATURE REVIEW

Tran CN,[1] Huang CJ,[1] Sun RM,[1] Hall MC,[1] Somani A,[1] Alety N,[1] Chheang M,[1] Afghani B[1,2]. [1]*University of California, Irvine, Irvine, CA;* [2]*CHOC Children's Hospital, Orange, CA.*

10.1136/jim-2016-000365.253

Purpose of Study Research on the efficacy of utilizing antacids to treat GERD in infants is scant. The purpose of

Abstract 253 Table 1

Author, Year	Group Size	Age	Drug Used	Duration of Study	Outcome	P-Value
Del Buono, R., 2005	20	34–319 days	Gaviscon	24 hours	PH measurement of reflux height (66% vs 77.3%)	0.001
Moore, D. J., 2003	30	3–12 months	Omeprazole	4 weeks	Clinical: Reflux index 8.9%+/−5.6%, vs. -1.9% +/−2.0%	<0.001 but no difference in irritability
Orenstein, S. R., 2009	162	1–12 months	Lansoprazole	4 weeks	Clinical 54% vs. 54%	P=NS P=0.032 for lower respiratory infections
Sutphen, J. L., 1986	19	1–12 months	Maalox	2 doses	PH measurement Pre and Post Antacid lower only if given with feeds	0.06
Winter, H., 2010	128	1–11 months	Pantoprazole	6 weeks	Clinical: There was no difference in withdrawal rates due to symptom worsening (pantoprazole 6/52; placebo 6/54) in double blind phase	0.09 in favor of antacid during week 5
Winter, H., 2012	98	1–11 months	Esomeprazole	6 weeks	Clinical: There was no difference in withdrawal due to symptom worsening (Esomeprazole 38.5% vs placebo 48.8%)	0.28

this study is to gather the existing data from clinical trials performed on infants to determine whether the use of antacids for the treatment of GERD in infants is deemed effective.

Methods Used We conducted a literature review through PubMed and Google Scholar. Only prospective studies with controls that included full-term infants less than 1 year of age were considered eligible.

Summary of Results We found 6 prospective studies that fulfilled the inclusion criteria. Results are summarized in the table. Two studies that used PH monitoring after a few doses of antacids showed some improvement in reflux. Majority of studies that measured clinical outcome did not show a difference between antacids and placebo groups. One study showed increased incidence of lower respiratory infections in the antacid group.

Conclusions Our literature review does not support the use of antacids in full-term infants with GERD. The limitations of the studies included small sample sizes, differing severity, different methods used to measure effectiveness, and various dosages of antacids. Further large placebo controlled studies are needed to determine the safety as well as the efficacy of antacids in infants.

Genetics
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

254 NOVEL GENOTYPE AND CLINICAL OUTCOME WITH ETIDRONATE THERAPY IN A NEONATE WITH GENERALIZED ARTERIAL CALCIFICATION OF INFANCY

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10.1136/jim-2016-000365.254

Introduction Generalized Arterial Calcification of Infancy (GACI) is a recessively inherited, extremely rare and frequently fatal disease. The condition is caused by mutations of ENPP1 or ABCC6 and has a phenotype of widespread calcification of large and mid-sized arteries in affected patients. Furthermore, myointimal proliferation leads to arterial stenosis and foci of periarticular calcifications. We report the clinical outcome in an infant with compound heterozygote mutations of ENPP1 who was on Etidronate therapy.

Case Report Our patient was born at term by emergent C-section for non-reassuring heart rate and was transferred to our center for concerns of respiratory distress. The pregnancy was uncomplicated.In the first week of life, he went to develop severe hypertension and congestive heart failure. His Echocardiogram revealed a moderate sized PDA and a severe dilated cardiomyopathy secondary to hypertension. He was treated with propranolol, amlodipine, furosemide and captopril for his hypertension.

Ultrasound imaging demonstrated the presence of extensive calcification in the aorta, renal vessels and splenic artery consistent with GACI. Genetic testing revealed 2 variant alleles in ENPP1: (1) a nucleotide change, c.2735T>C and (2) a 3.4 Kb deletion involving exon 6. At one month of age, he was started on etidronate therapy at 15 mg/kg/day and was maintained on this for 2 years. At age of 2 years, CT imaging showed resolution of vascular calcification and etidronate was discontinued. Repeat imaging at 1 year post discontinuance of etidronate shows no residual calcification within aorta and renal vasculature. He remains on captopril and propranolol for control of hypertension.

Conclusions We report an infant with novel compound heterozygote mutations of ENPP1 with vascular calcification demonstrating GACI phenotype who survived the neonatal period. GACI is frequently fatal condition in infancy. This patient was treated with Etidronate in infancy. It was tolerated well and he has not had recurrence of vascular calcification after cessation of etidronate. Further studies are needed to clarify the nature of the gene variants and the utility of etidronate in this condition.

255 PRECISION GENOMICS IN THE DIAGNOSIS OF SYNDROMIC VITREO-RETINOPATHIES

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10.1136/jim-2016-000365.255

Purpose of Study Many vitreoretinopathies present first to the eye clinic, however, a number of them have systemic manifestations. We sought to evaluate the role of targeted Next Generation Sequence (NGS) analysis and microarrays in accurate genetic diagnosis of Vitreo-retinopathies.

Methods Used We analyzed patients who had molecular testing in the Emory Genetics Lab for Stickler syndrome or vitreo-retinopathy between 2010 and 2015. We looked at their detailed clinical information from medical records when evaluated at Emory Ophthalmic Genetics Clinic.

Summary of Results We identified 44 individuals who had genetic testing for vitreo-retinopathy or Stickler syndrome. 17/44 (~39%) had definitive pathogenic mutations, majority 13/44 (30%) caused by mutations in the *COL2A1* gene and 3/44 (6%) caused by *COL11A1* gene causing Stickler syndrome. One individual had deletion of an exon in *VCAN* gene that causes Wagner's vitreoretinopathy confirming the suspected clinical diagnosis. Another individual had deletion of entire *COL2A1* gene identified by chromosomal microarray (ordered based on clinical presentation of developmental delays and Stickler syndrome). Six other individuals had Variants of unknown significance (VOUS) in *COL2A1* gene.

Conclusions Targeted genetic testing by NGS panels alone identifies definitive cause in nearly 33% of the individuals. Adding targeted microarray or chromosomal microarray to detect deletions and duplications based on strong clinical suspicion of a syndrome when NGS panel testing is negative adds significantly to positive test results~43% (3/7 positive arrays). The deletion of an exon as causative in *VCAN* gene is the *first* deletion reported in Wagner's syndrome. Our study suggests that NGS panels with genes that include syndromes with similar clinical presentation such as Stickler and Wagner's together (given the same test cost with NGS panels) and reflex testing by microarrays if NGS panel is negative is a very efficient precision genomics approach. Identifying definitive genetic etiology helps in early recognition of syndromes and prophylactic management of associated systemic conditions.

256 CLINICAL AND MOLECULAR CHARACTERIZATION OF SITUS INVERSUS TOTALIS DUE TO A FRAMESHIFT MUTATION IN *OFD1*

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10.1136/jim-2016-000365.256

Case Report Situs inversus totalis (SIT) is a pattern of malformation in which the major viscera are located in mirror image position compared with their typical location. Primary ciliary dyskinesia (PCD) accounts for 25% of SIT cases. Herein we describe the clinical and molecular features of a child with SIT due to a frameshift mutation in *OFD1*. We also review the broad phenotypic spectrum associated with mutations in *OFD1*.

A 10 month old male presented with SIT and persistent wheezing. There was a family history of learning problems in the mother and maternal aunts. He had dextrocardia with normal intracardiac anatomy and mirror image reversal of other viscera. A brain MRI was normal. He was macrosomic (weight z-score +3.81, length z-score +2.95). Physical exam revealed 2 posterior hair whorls, epicanthal folds, diffuse expiratory wheezing, palpable liver on the left, and mild motor and speech delays. Nasal scrapings showed no morphologic ciliary abnormalities. A targeted next generation sequencing panel for PCD genes revealed a hemizygous pathogenic frameshift variant in *OFD1* at Xp22.2 (c.3868del, p.Pro957Leufs*2).

Mutations in *OFD1* cause multiple allelic X-linked disorders, including Oral-Facial-Digital Syndrome Type 1, Simpson-Golabi- Behmel syndrome Type 2, Joubert syndrome Type 10 and a syndrome of macrocephaly, mental retardation and ciliary dysfunction.[1] Thoracic situs inversus but not SIT has been reported with an *OFD1* frameshift mutation[2]. Truncating loss of function mutations including frameshift mutations are a common pathogenic mechanism in *OFD1*- related disorders. The OFD1 protein is a component of the centrosome, which is important for ciliary formation and cell polarity and left-right axis patterning during embryonic development. Other genetic factors including modifying genes and environmental influences may play a role in mediating the divergent phenotypes associated with *OFD1* mutations.

REFERENCES

1 Budny *et al*. *Hum Genet*. 2006;120:171–178.
2 Thauvin-Robinet *et al*. *Clin Genet*. 2013;84:86–90.

257 KAUFMAN OCULOCEREBROFACIAL SYNDROME: A NOVEL MUTATION IN UBE3B IN TWO SIBLINGS AND ADDITIONAL PHENOTYPIC FEATURES

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10.1136/jim-2016-000365.257

Case Report Kaufman oculocerebrofacial syndrome (KOS) is a recognizable pattern of malformation also known as Blepharophimosis-Ptosis-Intellectual-Disability (BPID) syndrome. It is an autosomal recessive disorder, with only 14 cases reported to date. Features include significant developmental delay, hypotonia, postnatal growth retardation, microcephaly, distinctive facial features. This report describes a pair of siblings of Samoan ethnicity with KOS caused by a homozygous novel mutation in the ubiquitin-protein ligase E3B (UBE3B) gene.

A 3-year-old girl and her full sibling, a 6-month-old boy share a very similar phenotype of significant postnatal growth retardation. Both have microcephaly, hypotonia, cleft palate, atrial septal defect, and genital hypoplasia. They have distinctive facial features including blepharophimosis, upslanted palpebral fissures, epicanthal folds, small

posteriorly rotated ears, micrognathia and long fingers. The brother has more severe mandibular hypoplasia resulting in Pierre Robin sequence that required mandibular distraction at 6 months. In addition, the brother has other structural anomalies including intestinal malrotation that required surgery, periventricular heterotopia, vermian/pontine hypoplasia and an ectopic pituitary. Both children had feeding difficulties requiring gastrostomy tube feedings. Both children have global developmental delay and a profound mixed hearing loss. In both siblings, whole exome sequencing identified homozygous pathogenic splice variant in *UBE3B* (c. 2569–1 G>C), predicted to disrupt splicing.

This report brings to 16 the number of cases of KOS described in the literature. Several novel features presented in these siblings. The brother has additional structural malformations including intestinal malrotation and CNS anomalies not previously reported in KOS. While cleft and micrognathia are a recognized feature of KOS, this is the first description of severe mandibular hypoplasia resulting in Pierre Robin sequence. This report expands the phenotype description of this rare and clinically distinctive condition.

258 VARIABLE EXPRESSIVITY IN ALSTRÖM SYNDROME

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10.1136/jim-2016-000365.258

Purpose of Study Alström syndrome is an autosomal recessive condition characterized clinically by obesity, dilated cardiomyopathy, progressive hearing and vision loss, short stature, and type 2 diabetes mellitus. The disorder is rare with estimates of prevalence ranging from 1:10,000 to 1:1,000,000. This condition is due to mutations in *ALMS1* with the majority of described mutations predicted to cause premature protein truncation. Given the rarity of the disorder, the phenotypic variability is not well known. We are not aware of any previous scientific reports of twins with Alström syndrome. Our objective was to describe the phenotypic discordance and concordance of a set of twins with Alström syndrome.

Methods Used The data presented are based on retrospective chart review of twins with features of Alström syndrome and review of published cases.

Summary of Results Monozygotic twins presented with signs of congestive heart failure and were both found to have dilated cardiomyopathy (DCM) at 5 weeks of age. A dilated cardiomyopathy panel was obtained and found to be negative for any pathogenic mutations. At 23 months of age, the infants were concordant for nystagmus, cone-rod dystrophy, developmental delay, features of autism spectrum disorder, and normal hearing. The infants were discordant for the clinical course of the DCM with one progressing to worsening DCM, while the other spontaneously improved. The twins were also discordant for obesity with one twin having BMI and weight >> 99th centile while the other had normal weight and BMI. Subsequent sequencing of one twin identified pathogenic compound heterozygous mutations in the ALMS1 gene (c.2816T>A; c.10837_10838delCA).

Conclusions These data suggest that Alström syndrome has variable expressivity particularly with DCM and obesity and that stochastic events contribute to some of the phenotypic variability of Alström syndrome. Clinical laboratories should consider adding the ALMS1 gene to dilated cardiomyopathy panels. More studies of discordant sibs as well as mouse models are needed to further understand the disease mechanisms in Alström Syndrome.

259 ZEBRAFISH AT THE BEDSIDE: IN VIVO VALIDATION OF HUMAN DISEASE SEQUENCE VARIANTS

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10.1136/jim-2016-000365.259

Purpose of Study To provide rapid *in vivo* validation of suspected disease-causing mutations in critically ill human patients via use of a customizable vertebrate animal disease model.

Methods Used We use next-generation Illumina sequencing of patient-parent trios coupled with a custom bioinformatic analysis pipeline in order to identify likely causative disease variants. Details regarding patient recruitment, analytical pipeline, and metrics for clinical impact will be presented, including methods for identification of causative genes and variants of unknown significance to be selected for downstream *in vivo* validation.

Summary of Results The Rady Children's Institute for Genomic Medicine was founded in 2015 with a generous gift of $120 million dollars. Recent breakthroughs in the speed and affordability of whole-genome sequencing have enabled the rapid sequencing of critically ill patients in a timeline that could impact their hospital stay. As approximately 100 *de novo* changes occur per genome, our ability to determine which of these changes is likely to cause or contribute to the patient's disease is limited. Often, the disease mutation cannot be initially pinpointed from sequence data and bioinformatic approaches alone, but yields a list of potential candidates. In these cases, a rapid functional assay is required to definitively demonstrate causality, with *in vivo* models preferable to *in vitro* assays due to better approximation of the complex human embryonic/fetal environment.

Conclusions We have recently launched whole genome sequencing in the neonatal and pediatric intentive care units (NICU/PICU), with a focus on neurological disorders (e.g., seizure, autism, neurodevelopmental delay). We aspire to provide "actionable" sequencing results, with appropriate changes in therapy and/or disposition, to families of critically ill children whose unederlying disease etiology is genetic in origin. The zebrafish is a useful disease model for rapid assessment of the effects of novel mutations in a biological context.

260 USE OF FLOW CYTOMETRY FOR DIAGNOSIS OF EPILEPSY ASSOCIATED WITH HOMOZYGOUS *PIGW* VARIANTS

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10.1136/jim-2016-000365.260

Purpose of Study Compound heterozygous mutations in *PIGW* have been reported once previously in an individual with infantile spasms and hyperphosphatasia. *PIGW* encodes for a protein involved in the third step of glycosylphosphatidylinositol (GPI) synthesis. GPI anchored proteins are increasingly being recognized as important structures for cellular interactions and neuronal development. The purpose of the study is to investigate the use of flow cytometry as a functional tool to demonstrate decreased surface expression of GPI anchored proteins, support a genotype-phenotype correlation and confirm the diagnosis.

Methods Used Physical exam, detailed history, medical literature review, alkaline phosphatase levels, expanded epilepsy panel and flow cytometry.

Summary of Results An 8-month-old female presented with infantile spasms, myoclonic seizures, cortical visual impairment, developmental delay and minor dysmorphic features (brachycephaly, anteverted nares, tented upper lip, digital flexion contractures, pectus excavatum). Metabolic evaluation and brain MRI were normal. Alkaline phosphatase levels ranged from normal to mildly elevated. She was found to be homozygous for a variant in exon 2 of *PIGW* (c.199C>G; p.Pro67Ala) which was classified as unknown significance. The variant is in a conserved position and is uncommon in humans. Flow cytometry showed more than 60% decrease in cell surface expression of CD16 and CD24 and an 82% decrease in FLAER expression on granulocytes. There was also a 42% decrease in CD59 and 81% decrease in FLAER expression on lymphocytes as well as an 88% decrease in CD14 on monocytes. All values were compared to adult control. These results are consistent with the flow cytometry results from the previous case report of a patient with compound heterozygous mutations in *PIGW.*

Conclusions This is the second case reported and provides further evidence of an autosomal recessive *PIGW*-associated epilepsy. This report helps expand the phenotype of GPI anchored protein deficiencies, and shows that flow cytometry can potentially provide functional evidence and help clarify the diagnosis in suspected cases.

261 MIND THE GAP: SYNGAP1 AND RASOPATHIES

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10.1136/jim-2016-000365.261

Purpose of Study The RASopathies are a defined group of neurodevelopmental disorders which may be associated with multiple congenital anomalies and a predisposition to cancer. RASopathies can be caused by several pathogenetic mechanisms that ultimately impact or alter the normal function and regulation of the Ras/mitogen-activated protein kinase (MAPK) pathway. These pathogenetic mechanisms can include functional alteration of GTPases, Ras GTPase-activating proteins, Ras guanine exchange factors, kinases, scaffolding or adaptor proteins, ubiquitin ligases, phosphatases and pathway inhibitors. Although these mechanisms are diverse, the common underlying biochemical phenotype shared by all the RASopathies is Ras/MAPK pathway activation.

Methods Used RasGAPs (GTPase-activating proteins) are negative regulators of the Ras/MAPK pathway. Haploinsufficiency in neurofibromin (encoded by the *NF1* gene) and p120 RasGAP (encoded by the *RASA1* gene) are both examples of RasGAPs and cause neurofibromatosis type 1 (NF1) and capillary malformation-arteriovenous malformation (CM-AVM) syndromes, respectively. SYNGAP1 (synaptic Ras GTPase activating protein 1) is a more recently described RasGAP thought to be selectively expressed only in neurons.

Summary of Results Germline mutations in the *SYNGAP1* gene have been described and associated with Autosomal Dominant Intellectual Disability Type *5*, a non-syndromic intellectual disability that has not been thought of as part of the RASopathies. Here we present two individuals with pathogenic germline nonsense mutations in SYNGAP1 identified through exome sequencing and further expand upon the SYNGAP1 phenotype. With this, we present this as a new RASopathy based on the identification of causative mutations in this new RasGAP gene with neuronal-restricted expression understanding that it has a unique neurologically-centered clinical phenotype which does overlap phenotypically with other RASopathies.

Conclusions Therefore, not only do RASopathies include NF1, Noonan syndrome, Noonan syndrome with multiple lentigines, CM-AVM syndrome, Costello syndrome, cardio-facio-cutaneous syndrome and Legius syndrome, but we propose SYNGAP1 as an expansion of the RASopathies.

Neonatal Pulmonary III
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

262 DIFFERENTIATION OF MESENCHYMAL STEM CELLS INTO AIRWAY EPITHELIUM FOR USE IN A PORCINE MODEL OF LUNG INJURY

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10.1136/jim-2016-000365.262

Purpose of Study Multipotent mesenchymal stem cell (MSCs) use in tissue healing has gained considerable interest. MSCs are being evaluated in clinical trials for a variety of diseases. Our objective was to demonstrate differentiation of porcine-derived MSCs to small airway epithelial cells (SAEC) and investigate the ability of undifferentiated MSCs vs MSCs pre-differentiated into SAECs to provide

improvement in lung function in a neonatal porcine model of acute lung injury (ALI).

Methods Used MSCs were isolated from adipose and bone marrow from swine, cultured, and characterized according to consensus criteria. MSCs were differentiated into SAECs by culturing in media designed for human SAECs. SAECs were characterized using immunofluorescence (IF) detection of cell surface markers and surfactant proteins, and by morphologic evaluation. ALI is produced in 7–8 kg pigs by injecting oleic acid to disrupt alveolar surfactant causing pulmonary hemorrhage and edema. Undifferentiated vs pre- differentiated MSCs will be administered via the pulmonary artery or broncohoalveolar lavage to compare effect of delivery route on localization to site of injury. After treatment, lung function will be assessed up to 6 hours.

Summary of Results We isolated MSCs from bone marrow and adipose from 17 pigs. MSCs were differentiated into SAECs, verified by morphological comparison against standard human SAECs. IF showed positivity for clara cell secretory protein and surfactant proteins B and C. After differentiation, cell growth terminated. We found that MSCs must be amplified in the undifferentiated state then differentiated to achieve SAECs for *in vivo* dosing. To provide consistent dosing of MSCs for ALI treatment, we developed procedures for amplification and storage in 2 million MSC aliquots, and addition of a fluorescent marker in the cells for histological tracking of MSC delivery to the injury.

Conclusions MSCs obtained from various tissue sources can be differentiated into small airway epithelial cells. We developed a production strategy to minimize dosing variability. Comparing administration route will help determine if restoration of a physical cell barrier is sufficient, or if surfactant production is needed for recovery of pulmonary function.

263 IGF1 SIGNALING & DOWNSTREAM TARGETS ARE REQUIRED FOR ALVEOLAR FORMATION

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10.1136/jim-2016-000365.263

Purpose of Study Bronchopulmonary Dysplasia, BPD remains a common morbidity in preterm infants. Its etiology likely involves arrested alveolar development. We isolated secondary crest myofibroblasts (SCMF), a key cell type in alveolar formation, and used unbiased transcriptomic analysis to show increased gene expression in the IGF1 signaling pathway, including CCN1 a matricellular protein. Here, we combined a clinically relevant preterm lamb model with a gene targeted analysis in mouse to investigate the role of IGF1 signaling in lung development & disease.

Methods Used Lamb lungs were from Dr. Kurt Albertine (University of Utah). Mouse experiments & tissue procurement were strictly compliant to USC, IACUC regulations. *Ccn1(floxed)* mice were from Dr. L. Lau (University of Illinois, Chicago). RNA extraction was by the Trizol method. Quantitative RT-PCR was performed per our published protocols (Li *et al.*, 2015).

Summary of Results *Igf1* mRNA was measured in preterm lambs treated with 2 modes of ventilation. Lung Igf1 was repressed by mechanical ventilation (MV) & noninvasive high frequency ventilation (HFNV) compared to term. A downstream target of IGF1 signaling, *Ccn1*, increased during alveogenesis in mice & sheep. We generated mesodermal-specific *Ccn1* mutants, designated $Ccn1^{dermo1}$. $Ccn1^{dermo1}$ mice were born alive with birth weight similar to control siblings. By one month, $Ccn1^{dermo1}$ mice weighed only 46% of controls with overt respiratory distress. Lung histology at PN 7 showed alveolar simplification akin to human BPD. The endothelial progenitor marker *Flk1* was decreased in $Ccn1^{dermo1}$ lungs as was *Pdgfr-alpha* a critical regulator of alveogenesis. *Ccn1* mRNA was repressed in preterm lambs treated acutely with MV compared to HFNV. However, chronic ventilation with either strategies repressed *Ccn1* significantly.

Conclusions The studies described here reveal the key role of IGF1 network and its downstream target CCN1 in alveolar formation in a clinically relevant lamb model of BPD. Supported by NIH, NHLBI & The Hastings Foundation.

264 EXTRAUTERINE GROWTH RESTRICTION DOES NOT ALTER LUNG ELASTIN PROTEIN ABUNDANCE IN JUVENILE RATS

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10.1136/jim-2016-000365.264

Purpose of Study Preterm infants are at risk for extrauterine growth restriction (EUGR). EUGR predisposes preterm infants to chronic lung disease or bronchopulmonary dysplasia (BPD). BPD is characterized by decreased lung compliance. Decreased lung compliance results, in part, from increased lung elastic fiber deposition. We showed that EUGR in the rat leads decreased compliance. However, the effect of EUGR on rat lung elastin is unknown. We hypothesize that EUGR will increase elastin protein abundance in the lung of juvenile rats.

Methods Used We induced EUGR in a rat model using variation in litter size by cross fostering newborn rat pups into rat dams with litter sizes of 16 (EUGR) or 8 (control). Rat pup weight was measured every other day from birth to day of life 21 (d21). At postnatal d21, rats were killed and lung elastin measured by western blot.

Summary of Results Results are EUGR as a percentage of sex-matched control±SD (*=$p<0.05$). Rat pups in the EUGR group weighed significantly less (75±3%*) than control by postnatal d5 and continued to weigh less through d21 (70±5%*). EUGR did not alter lung elastin protein abundance in male or female rat lung. However, levels of lung elastin protein abundance were less in female control lungs compared to male control lungs (48±11%, $p\leq0.05$).

Conclusions Contrary to our hypothesis, EUGR does not alter elastin protein abundance in the lung of male juvenile

rats. Given the previously observed decreased lung compliance in EUGR rats, we speculate that EUGR may alter other determinants of elastic fiber deposition in the lung. We are currently quantifying levels of molecules that assemble elastic fibers, as well as elastic fiber deposition in the EUGR rat lung using Hart's Stain.

265 INSULIN-LIKE GROWTH FACTOR-1 IN ALVEOLAR FORMATION IN PRETERM LAMBS

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10.1136/jim-2016-000365.265

Purpose of Study Insulin-like growth factor 1 (IGF1) is an important morphogen during development and after birth. Plasma IGF1 protein level is low in preterm human infants and lambs compared to fetal development. Also, IGF1 mRNA level is low in lung tissue of ventilated preterm human infants who died early in postnatal life. We recently showed that preterm lambs supported by invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV) for 3d have lower IGF1 mRNA levels than lambs at term gestation. IMV is associated with alveolar simplification whereas NIV is associated with alveolar formation and somewhat higher level of IGF1 mRNA in the lung. To begin to identify the role of IGF1 in alveolar formation, we treated preterm lambs with IGF1 receptor (R) antagonist or agonist. We asked whether proliferation and apoptosis of mesenchymal and epithelial cells is affected according to intervention.

Methods Used Lung tissue was used from 4 preterm lamb groups: (1) IMV (bad lung outcomes), (2) NIS (good lung outcomes), (3) IMV plus IGF1 R-antag (poorer gas exchange than IMV), and (4) NIV plus IGF1 R-agon (similar gas exchange to NIV). First treatment was mixed in surfactant. Subsequent treatments at 24 h intervals were nebulized. We used immunohistochemistry and morphometry to identify proliferating and apoptotic indices for mesenchymal/100 distal airspace epithelial cells and similarly for epithelial cells/100 mesenchymal cells.

Summary of Results Downstream signaling molecules were decreased or increased, respectively, for IGF1 R-antag and R-agon in the lung. Parenchymal architecture indicated heterogeneous distribution of the treatment agents, meaning patchiness of distal airspace wall thickness; therefore, quantitative measurements were made on the thickest and thinnest walls. For the IMV plus IGF1 R-antag group, thickest walls had more proliferation and less apoptosis of both mesenchymal cells and epithelial cells compared to IMV. For the NIV plus IGF1 R-agon group, thinnest walls had less proliferation and more apoptosis of both mesenchymal cells and epithelial cells compared to NIV.

Conclusions Our results provide molecular mechanistic support that IGF1 is involved in alveolar formation in chronically ventilated preterm lambs. Current studies are reversing the treatment strategies. HL110002, HL062875, HL07744

266 VITAMIN D_3 BLOCKS HYPEROXIA-INDUCED TRACHEAL SMOOTH MUSCLE CELL PROLIFERATION AND DIFFERENTIATION

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10.1136/jim-2016-000365.266

Purpose of Study Childhood asthma is characterized by increased lung and tracheal smooth muscle (TSM) mass. Although alveolar smooth muscle differentiation has been studied extensively, there is not much information on TSM differentiation. Since perinatal vitamin D deficiency has been proposed to be an important contributor of childhood asthma, we hypothesize that vitamin D_3 supplementation, in addition to its effects on alveolar smooth muscle differentiation (Sakurai *et al*, Am J Physiol Lung Cell Mol Physiol. 2009), blocks neonatal TSM cell proliferation and its differentiation to a myogenic phenotype.

Methods Used Using standard methods, TSM cells were isolated from postnatal day 1 Sprague Dawley rat pups. At 80–90% confluence, cells were exposed to either normoxia (21% O_2) or hyperoxia (95% O_2)±vitamin D_3 (10^{-7}M) for 24 h. Subsequently, cell proliferation (thymidine incorporation and Western analysis for cyclin D1), apoptosis (Western analysis for p-Caspase-3, BcL2, and Bax), and myogenic differentiation (Western analysis and immunocytochemistry for α smooth muscle actin (SMA), fibronectin, calponin, and Wnt pathway intermediates LEF-1 and β-catenin) were examined. To investigate the underlying mechanisms, regulators of TSM cell proliferation and differentiation, MAP kinases (p38, ERK1/2, JNK) and PKC activation were determined.

Summary of Results Exposure to hyperoxia resulted in **1)** increased apoptosis (increased p-Caspase 3; decreased BcL2/Bax ratio); **2)** myogenic differentiation (increased protein levels of αSMA, fibronectin, calponin, LEF-1 and β-catenin); **3)** MAPK and PKC activation ($p<0.05$ vs. control, for all); and **4)** vitamin D_3 pretreatment blocked almost all of these effects.

Conclusions Exposure to severe (95% O_2) hyperoxia results in TSM cell apoptosis and increased differentiation to a myogenic phenotype, likely mediated via MAPK and/or PKC activation. Vitamin D_3 effectively blocks these effects, reinforcing the need for adequate vitamin D levels during lung development to prevent childhood asthma. However, the effects of exposure to mild-moderate hyperoxia and the centrality of MAPK vs. PKC activation in mediating vitamin D's blockage of hyperoxia-induced effects on TSM cells are not yet established. [Grant Support: HL107118; HL27137, HD71731; TRDRP: 23RT-0018]

267 INVASIVE MECHANICAL VENTILATION DECREASES ILEAL FABP2 MRNA IN PRETERM LAMBS

Pyne AL, Wang H, Ruybal L, Dong L, Dahl M, Albertine K, Joss-Moore L. *University of Utah, Salt Lake City, UT.*

10.1136/jim-2016-000365.267

Purpose of Study Premature neonates supported by invasive mechanical ventilation (IMV) are at increased risk of

developing necrotizing enterocolitis (NEC). NEC is characterized by disruption to the immature intestinal barrier and enterocyte damage. We showed that preterm lambs managed for 21 days by IMV develop a NEC-like phenotype, and have decreased ileal PPARγ protein expression compared to preterm lambs managed by non-invasive support (NIS). PPARγ is involved in gut maturation and PPARγ agonists are protective against NEC. A transcriptional target of PPARγ, also important for enterocyte development, is intestinal fatty acid binding protein 2 (FABP2), which transports long-chain fatty acids into the nucleus, thus activating PPARγ. The effects of IMV on ileal FABP2 are unknown.

We hypothesize that preterm lambs managed by IMV for 21 d will have lower ileal FABP2 mRNA levels than preterm lambs managed by NIS for 21 d.

Methods Used Preterm lambs were managed by IMV or NIS for 21 days (to term-equivalent age). Both groups received ewe's colostrum for the first 3 days of life and then ewe's mature milk for the remainder of the study. Reference group was unventilated normal term lambs. Real-time PCR was used to measure FABP2 mRNA levels in ileum.

Summary of Results Ileal FABP2 mRNA levels were less in IMV lambs than in NIS lambs (8±12%, $p \leq 0.05$). Compared to term normal lambs, IMV decreased FABP2 mRNA levels (20±16%, $p \leq 0.05$). However, compared to term normal lambs, NIS did not significantly alter FABP2 mRNA levels (77±20%, $p = 0.36$).

Conclusions We conclude that 21 days of IMV decreases ileal FABP2 mRNA levels in preterm lambs. We speculate that decreased ileal FABP2 mRNA in IMV lambs results in part from the decreased FABP2 driven transactivation PPARγ and reduced fatty acid availability in enterocytes.

Neonatology – Perinatal Biology I
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

268 DISCOVERY OF NOVEL HYPOXIA-PROTECTIVE AND HEAT-PROTECTIVE GENES USING A ZEBRAFISH DISEASE MODEL

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10.1136/jim-2016-000365.268

Purpose of Study To establish a novel disease model in zebrafish where mechanisms of hypoxia- and heat-resistance could be investigated using genetic, genomic, and pharmacologic methods.

Methods Used Physiologic and metabolic adjustment to environmental stress, such as hypoxia and heat shock, is ubiquitous across nature. Insight into the genetic components of the hypoxia and heat stress responses were facilitated by the discovery and characterization of hypoxia-inducible factor (HIF-1a) and heat shock proteins in the 1980's. In order to identify novel hypoxia- and heat-protective genes, we established stress parameters during embryogeneis/organogenesis and performed transcriptomic studies in a novel embryonic zebrafish stress model. Our transcriptomic studies identified multiple novel stress-induced genes, which were individually validated by quantitative PCR and/or in situ hybridization. We then performed knockdown and/or targeted knockout studies to show that these genes are required for hypoxia protection (*irs2, crtc3, btr01*) as well as heat stress protection (*cbx*, *chord*, *bag-a*, *bag-b)*.

Summary of Results The hypoxia-response genes *irs2* and *crtc3* are metabolic regulators of insluin/glucose signaling and fatty acid storage, respectively. We have generated targeted mutants in both genes and are in the process of analyzing metabolic differences at baseline and after hypoxia exposure. Interestingly, the heat-protective gene *cbx* is expressed only in neurons and is predicted to be a component of the chromatin-repressive Polycomb complex. Preliminary analyses of null *cbx* mutants reveal heat sensitivity, with dramatic increases in neuronal cell death and overall embryonic death in response to mild heat stress.

Conclusions These results extend our understanding of the genetic mechanisms of hypoxia- and heat-protection and affirm the discovery potential of this novel vertebrate stress model in zebrafish.

269 PRENATAL ALCOHOL EXPOSURE EXACERBATES CHORIOAMNIONITIS: A PRECLINICAL INVESTIGATION

Maxwell J, Davies S, Yellowhair T, Savage D, Jantze L. *University of New Mexico, Rio Rancho, NM.*

10.1136/jim-2016-000365.269

Purpose of Study Roughly 200,000 infants born annually in the United States are impacted by prenatal alcohol exposure (PAE), with lifelong neurodevelopmental sequelae including attention deficit disorders, seizures, and cognitive deficits. These infants also have a five-fold increased rate of chorioamnionitis (CHORIO), the most common placental abnormality in spontaneous preterm birth and encephalopathy of prematurity. Although clinically related, the mechanisms leading to subsequent brain injury in PAE and CHORIO have not been studied in a validated animal model. We hypothesized that moderate PAE and CHORIO would result in significant deficits in myelination and white matter microstructure on magnetic resonance imaging (MRI).

Methods Used Pregnant Long-Evans rats were allowed to drink 5% ethanol or saccharin until embryonic day 17 (E17) to mimic moderate PAE. On E19 a laparotomy was performed with transient (30 min) uterine artery occlusion (transient systemic hypoxia ischemia, TSHI) followed by injection of lipopolysaccharide (LPS, 4 μg/amniotic sac) to mimic CHORIO. The laparotomy was closed and pups were born at E22. Pups matured with their dams until postnatal day 15 (P15) or P28 (n=36–49 per group). Kruskal-Wallis with Dunn's correction was used to assess difference in survival between groups, and one-way ANOVA with Bonferroni's correction for MRI data.

Summary of Results PAE+TSHI+LPS resulted in a severe injury concomitant with significantly increased fetal mortality and reduced postnatal survival ($p < 0.05$). Specifically, the combination resulted in 95% fetal mortality and death

of live born offspring by P2. This fetal and postnatal mortality was significantly greater than that observed in either PAE (3% mortality) or TSHI+LPS (57% mortality) alone. Animals with PAE+TSHI+LPS had reduced white matter fractional anisotropy and impaired axial and radial diffusion compared to sham.

Conclusions This is the first report that the combination of PAE and CHORIO results in a severe *in utero* insult concomitant with significant brain injury in surviving pups. Preclinical models recapitulating PAE in the setting of CHORIO will aid in the identification of interventions that may be used to reduce brain injury and chronic neurologic disabilities in children.

270 HUMANIN AND NOTCH-1 PARTNER IN PROLIFERATING NEUROEPITHELIAL CELLS DURING FETAL NEURODEVELOPMENT

Baldauf C, Shin B, Nakamura H, Lee K, Devaskar SU. *University of California, Los Angeles, Los Angeles, CA.*

10.1136/jim-2016-000365.270

Purpose of Study Many neurodevelopmental disorders are influenced by prenatal factors such as hypoxia, oxidative stress, and infection, all of which predispose to cellular apoptosis and death. Humanin (HN) is a 24 amino acid peptide with cytoprotective and anti-apoptotic properties in models of acute and chronic adult neurological disorders. The presence of HN and its role in fetal/neonatal brain development has yet to be systematically investigated. Our hypothesis is that HN plays a key role in fetal neurodevelopment with a propensity to be altered in neurodevelopmental disorders.

Methods Used Murine embryonic day 10–19 (E10–19) coronal brain sections (n=5) were immunostained for mouse HN (mHN) using anti-HN antibody (ab). Co-localization studies using markers for progenitor cells (Nestin), stem cells (SOX2), ependymal cells (Vimentin) and cell fate regulator Notch-1 examined cell-specificity of mHN at E19. Co-immunoprecipitation (Co-IP) experiments were performed using E19 whole brain lysates employing human brain tumor cells as a positive control for proliferation with anti-HN ab. Immunoprecipitates were Western blotted (WB) using anti-Notch-1 ab and imaged with chemiluminescence. Utilizing Nerve Growth Factor (NGF) treated PC12 cells as a neuronal differentiation model, the effect of exogenous HN peptide (HNG) on expression of HN and Notch-1 was examined by WB.

Summary of Results 1) HN found in fetal murine brain from E10–19 (term ~E21) localizes to CC and NEC regions; 2) HN co-localizes with Notch-1 at the apex of NECs, further confirmed by Co-IP of HN and Notch-1; 3) HN and Notch-1 are found in PC12 and human brain tumor cells, with exogenous HN exposure resulting in increased Notch-1 expression (~50%) vs controls.

Conclusions 1) Murine fetal brain begins expressing HN in CC and NECs early in development coinciding with the neural progenitor cell proliferative phase (E10); 2) HN co-localizes with Notch-1 in NECs with confirmed protein-protein interaction mimicking that seen in proliferating human brain tumor cells; 3) PC12 cells exposed to HNG demonstrate increased Notch-1 expression. We propose that HN in partnership with Notch-1 forms a major mediator of neural progenitor cell proliferation. Disruption of this key partnership may underlie certain neurodevelopmental disorders.

271 ADIPONECTIN PREVENTS OBESITY AND HEPATIC STEATOSIS IN MOUSE OFFSPRING BORN TO OBESE DAMS

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10.1136/jim-2016-000365.271

Purpose of Study Childhood obesity may have its origin in fetal life. Using a novel mouse model of maternal obesity with extensive similarities to the human condition, including low circulating adiponectin (ADN), we have demonstrated that ADN supplementation in obese pregnant dams prevents fetal overgrowth. We hypothesized that ADN supplementation during pregnancy attenuates the adverse metabolic outcomes in adult mouse offspring of obese dams.

Methods Used Female C57BL/6J mice were fed control or high-fat/high-sugar diets. Pregnant obese and control mice were given PBS or ADN (0.62 μg/g/d) infusion at E14.5-E18.5. Fasted male offspring were studied at 3 months (N=36). A glucose tolerance test (GTT) was performed. Serum insulin and triglycerides as well as hepatic triglyceride and glycogen deposition were measured. Hepatic neutral lipid deposition was determined by Oil Red O staining in frozen tissue sections. Hepatic perilipin-2 protein expression and hepatic insulin signaling (IR-β, AKT, GSK-3α) were measured by western blot. Hepatic gene expression of the insulin targets G6Pase, PEPCK, PGC-1α, SREBP-1, ACC, FAS, and glycogen phosphorylase were determined using RT-qPCR. Results were analyzed by one-way ANOVA and considered significant when $p<0.05$.

Summary of Results Male offspring of obese pregnant dams (OB/PBS) were 20% heavier than offspring born to both control pregnant dams (C/PBS) and ADN supplemented obese dams (OB/ADN). The GTT area under the curve (+25%), serum insulin (+2.4-fold), serum triglycerides (+46%), hepatic triglyceride content (+1.6-fold), hepatic neutral lipid staining (+5.5-fold), hepatic perilipin-2 protein expression (+1.7-fold), and hepatic glycogen deposition (+2-fold) were increased in OB/PBS offspring compared to C/PBS offspring. All of these metabolic aberrations were prevented in OB/ADN offspring. Hepatic insulin signaling activity and gene expression of insulin targets did not differ between groups.

Conclusions Adiponectin supplementation in pregnant obese dams prevented obesity, glucose intolerance, hypertriglyceridemia, and hepatic steatosis in adult male offspring born to obese dams. ADN may be a potential therapeutic agent for preventing the long-term metabolic consequences in offspring born to obese mothers.

272 MATERNAL TOBACCO SMOKE EXPOSURE DIFFERENTIALLY PROGRAMS CANNABINOID RECEPTOR EXPRESSION AND IN ADIPOSE TISSUE OF ADULT RATS

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10.1136/jim-2016-000365.272

Purpose of Study Maternal tobacco smoke (MTS) exposure programs the development of adult obesity. Obesity development depends in part on the endocannabinoid system (ECS). The ECS includes the type 1 cannabinoid receptor (CB1), which is expressed from the Cnr1 gene, and increased in obesity. We previously showed that fetal exposure to MTS programs the development of adult obesity in male, but not female rats. We also showed that in the weanling rat, before the onset of obesity, expression from the Cnr1 gene, and levels of CB1 protein, were altered in a sex-and depot specific manner in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). However, weather altered levels of Cnr1 mRNA and CB1 protein abundance persist in the adult rat after MTS is unknown. We hypothesized that fetal MTS exposure would alter Cnr1 mRNA and CB1 protein abundance in a sex- and depot-specific manner in adult male and female rat adipose tissue.

Methods Used Pregnant Sprague Dawley rats were exposed to tobacco smoke daily from embryonic day 11 to term. Pups were cross-fostered to a control dams, until d21. At d60, male and female VAT and SAT adipose tissue was collected. Cnr1 mRNA was measured by real-time RT-PCR and CB1 protein abundance was measured by western blot.

Summary of Results Results are reported as MTS as % of sex-matched control (*$p<0.05$). In VAT of adult male rats, MTS decreased Cnr1 mRNA (41±12%*) and CB1 protein abundance (38±36%*). In VAT of adult female rats, MTS did not significantly alter Cnr1 mRNA, but increased CB1 protein abundance (161±36%*). In SAT of adult male rats, MTS increased Cnr1 mRNA (188±52%*) and CB1 protein abundance (177±77%*). In SAT of adult female rats, MTS did not significantly alter Cnr1 mRNA, or CB1 protein abundance.

Conclusions MTS alters Cnr1 mRNA and CB1 protein abundance in rat adipose in a depot- and sex-specific manner in adult rats. We speculate that persistent increased expression of Cnr1 and CB1 protein in adult male SAT following MTS is the result of early epigenetic changes, and we are currently measuring DNA methylation of the Cnr1 gene.

273 INCREASED PLACENTAL FATTY ACID BINDING PROTEIN EXPRESSION IN A BABOON MODEL OF INTRAUTERINE GROWTH RESTRICTION

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10.1136/jim-2016-000365.273

Purpose of Study Multiple placental nutrient transport systems have been reported to be down-regulated in intrauterine growth restriction (IUGR) but fatty acid transport has not been studied in any detail. Previously we demonstrated up-regulation of placental fatty acid (FA) transport proteins in human IUGR (unpublished). Here we studied placental protein expression of fatty acid binding proteins (FABPs) across late gestation in a maternal nutrient restriction (MNR) baboon model of IUGR. We hypothesized that placental FABP expression is increased in IUGR.

Methods Used Pregnant baboons were fed control ad libitum or MNR diet (70% of control calories) from gestation day (GD) 30. Placentas were collected at GD120 (0.65 gestation (G); control n=8; MNR n=9), GD140 (0.75 G; control n=6; MNR n=7) and GD165 (0.9 G; control n=3; MNR n=6) and homogenized. Protein expression of FABP 1, 3, 4, and 5 was determined using Western blot. Statistical differences were assessed using student's *t*-test and Pearson's correlation.

Summary of Results Placental and fetal weights at GD120 and GD140 did not differ significantly between control and MNR groups. At GD165 placental (−17%, $p=0.01$) and fetal weights (−10%, $p=0.06$) were reduced in MNR vs control. Expression of placental FABPs was not different between the two groups at GD120 or GD140. However, at GD165 FABP1, FABP3, and FABP5 ($p<0.05$) expression was increased in MNR vs. control. Furthermore, FABP1 and FABP3 expression increased significantly across late gestation ($R^2=0.35$ and $R^2=0.49$, respectively; $p<0.05$) in the MNR group but not in control.

Conclusions Despite markedly different degrees of adiposity between the human (15%) and baboon fetus (5%), proteins involved in placental FA transport appear to be up-regulated in IUGR in both species, possibly representing an adaptive response to maintain delivery of critical fatty acids for brain growth. Further studies are required to demonstrate that these changes result in increased FA transport to the fetus.

Supported by P01HD021350.

Neonatology General III Concurrent Session 8:00 AM – 10:00 AM Friday, January 27, 2017

274 USE OF NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION IN NEONATAL UNITS IN THE UNITED STATES

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10.1136/jim-2016-000365.274

Purpose of Study To ascertain the practice of nasal intermittent positive pressure ventilation (NIPPV) in neonatal units in the United States.

Methods Used An online questionnaire on the use of NIPPV was distributed to members of the Section on Neonatal Perinatal Medicine of the American Academy of Pediatrics. Sample size of 353 was calculated a priori for a confidence interval of 95% and margin of error of 5%.

Abstract 274 Table 1 Maximum peak inspiratory pressure (cm H2O) used on NIPPV based on birth weight

Birth weight	20	22	24	26	28	30	>30
<1000 g	33.42%	16.58%	17.12%	12.50%	6.69%	9.51%	4.08%
1000–1500 g	18.26%	14.71%	24.25%	15.53%	10.08%	12.26%	4.90%
1500–2500 g	13.11%	10.38%	20.77%	17.49%	14.48%	15.03%	8.74%
>2500 g	11.85%	5.79%	18.46%	15.70%	12.40%	22.87%	12.95%

Summary of Results Responses were received from 416 Neonatologists practicing across 45 states in the United States. NIPPV was reported to be used by 88% of the respondents. The most frequently reported indication for NIPPV was to prevent post extubation failure in infant less than 26 weeks (51%). NIPPV was considered as a primary mode of respiratory support by 18% of respondents in infants less than 26 weeks gestation and in 25% infants between 26 and 30 weeks gestation. About 40% of respondents reported to always consider NIPPV for infants who had apnea while on CPAP before considering invasive mechanical ventilation. Fifty-five percent of the respondents used non-synchronized NIPPV. 22% of the respondents provided synchronized NIPPV via neurally adjusted ventilatory assist device, while 21% reported using flow synchronization. Fifty-four percent of respondents considered NIPPV to be associated with increased risk of abdominal distention compared to NCPAP, and would not use NIPPV in the immediate post operative period after abdominal surgery. RAM nasal cannula was used by 40% of the respondents, whereas 27% used short binasal prongs to provide NIPPV. The pressures used to deliver NIPPV varied widely (Table 1).

Conclusions NIPPV was used by majority of the respondents, mostly as a mode to prevent post extubation failure in extremely preterm infants. Over half of respondents report using non-synchronized NIPPV. The interface and pressures used to deliver NIPPV were variable among the respondents.

275 HIGH FLOW NASAL CANNULA FOR NEONATAL TRANSPORT

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10.1136/jim-2016-000365.275

Purpose of Study Noninvasive ventilation, including high flow nasal cannula (HFNC), provides effective neonatal respiratory support. Data is limited on HFNC use during neonatal transport. Following introduction of HFNC use in the NICU, our transport service adopted HFNC for neonatal transport. Our objective was to assess the safety and efficacy of HFNC during neonatal transport.

Methods Used 197 neonates transported on HFNC via a Neo Pod T system were identified from LifeFlight transport data in 2012–2013. Data included demographics, transport location, distance, indication, and mode; as well as pre-transport and intra-transport respiratory support data. We compared neonates that succesfully tolerated HFNC transport to those who required support escalation (defined as increase in flow ≥2 L/min or FiO2 ≥20%).

Abstract 275 Table 1

	Success (n, 172)	Escalate (n, 25)
Gestation (wk)	35.5 +/−4.1	35.5 +/−3.4
B Wt (g)	2600 +/−900	2800 +/−750
Age: 0–48 hrs (n, 138)	119 (86%)	19 (14%)
>48 hrs (n, 59)	53 (89%)	6 (11%)
Transport mode: Rotor (n, 44)	33 (75%)	11 (25)*
Fixed-wing (n,27)	25 (93%)	2 (7%)
Intra-hospital (n, 26)	24 (92%)	2 (8%)
Ground (n, 100)	90 (90%)	10 (10%)
Diagnosis: Respiratory (n, 110)	94 (85%)	19 (14%)
Anomaly/other (n, 87)	78 (90%)	6 (11%)
FiO2: Pick-up	0.45 (.28)	0.62 (.29)*
Drop-off	0.39 (.20)	0.64 (.24)*
SpO2/FiO2: Pick-up	280 (128)	195 (104)*
Drop-off	285 (107)	171 (88)*
NC flow, drop-off	3.8 (1.7)	4.8 (1.4)*

* P<0.05

Summary of Results 87% of neonates (172/197) were safely and effectively transported on HNFC. Demographic features and outcomes are shown in the Table. Infants requiring escalation had significantly higher pre-transport FiO2 and were more frequently transported by air. There were no air leak events related to HFNC transport.

Conclusions HFNC appears to be a safe, effective mode of respiratory support in transport of selected neonates. Safe, effective HFNC transport may be identified by certain parameters, including lower initial FiO2 and higher initial SpO2/FiO2 ratio.

276 NEONATAL INTUBATION COMPLICATIONS

Harris SJ, Krick J, Sawyer T, Gray M, Umoren R. *University of Washington, Moscow, ID.*

10.1136/jim-2016-000365.276

Purpose of Study Neonatal intubation is a procedure that requires interprofessional communication and teamwork. It is a common procedure and requires a team of (at minimum) a physician or advanced neonatal care provider, respiratory therapist, and registered nurse. There is a high risk of tracheal intubation adverse events (TIAEs). The purpose of this study was to determine incidence rates of TIAEs during neonatal intubation and to determine correlations of these TIAEs with patient identifiers and teamwork ratings.

Methods Used NEAR4NEOS is an IRB approved study to improve the quality of patient care in two level 4 NICU

centers. It is a prospective collection of data on neonatal tracheal intubation from 2/12/2015- 3/27/2016. This data includes demographic information, TIAEs, number of attempts, patient outcomes, and teamwork scores for 259 neonatal patients. We used this data to find correlations and incidence rates.

Summary of Results Data was gathered for 259 patients (135 male and 122 female). The average age of the patients was 26.6 days. The average gestational age was 29.3 (5) wks. Average birth and dosing weights were 1.5 (1.2) and 1.9 (1.3) Kg, respectively. For these patients, 514 intubations were attempted and 114 had complications (21.5%). The most common complications were esophageal intubation (65, 12.3%) and dysrhythmias (12, 2.3%). The Pearson correlation between intubation complications and overall teamwork ratings was −0.0822. Number of attempts, self-reported stress, dosing weight, and birth weight had the largest correlations with intubation complications, with Pearson coefficients of 0.475, −0.199, −0.159, and −0.135 (respectively). The correlation between TIAEs and night shifts was 0.008. Though nearly twice as many patients are intubated during day shifts than night shifts (174 and 91 patients, respectively), both shifts have 21.55% TIAE incidence rates.

Conclusions TIAEs are common in the NICU, occurring in approximately 21.5% intubation attempts. The majority of TIAEs in the NICU centers we studied were esophageal intubation and dysrhythmias. The correlation between teamwork ratings and TIAEs was very small. We anticipate this is because of the difficulty in accurately measuring teamwork ratings. Finally, tracheal intubation safety appears similar between day and night shifts.

277 IMPROVING NEONATAL INTUBATION OUTCOMES USING TEAMWORK TRAINING

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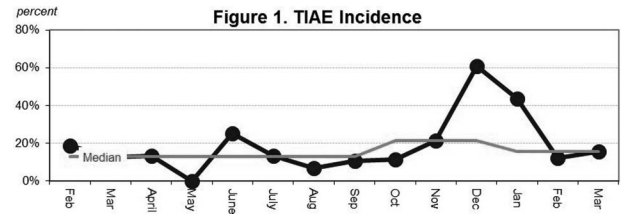
10.1136/jim-2016-000365.277

Purpose of Study Over 20% of neonatal intubations are complicated by tracheal intubation adverse events (TIAEs). In October 2015, a 50-bed level 4 NICU with 250 interprofessional staff began a teamwork training initiative based on the TeamSTEPPS program. The training was delivered in stages: leadership training (Oct 2015), virtual scenario development (Jan–Apr 2016), faculty/fellow training (May–Jun 2016), and staff training (Sep–Dec 2016). This study aims to evaluate the impact of teamwork training on TIAEs.

Methods Used The NEAR4NEOS database on neonatal tracheal intubation includes demographic data, TIAEs, and teamwork. Situational awareness, knowledge sharing, communication, and clear roles and responsibilities and teamwork are rated from 1 to 7. We used ANOVA and the Pearson correlation coefficient to analyze the data.

Summary of Results Data was gathered for 157 patients (331 intubation attempts). Mean patient age was 16.4 (27) d, and mean gestational age was 28.5 (4.5)wks. Mean birth and dosing weights were 1.3 (1.2) and 1.5 (1.1)kg, respectively. The mean gestational age was lower in the Oct–Dec 2015 period at 27.1 (3.0)wks but there were no differences in age at encounter, birth weight and dosing weight across the time periods. Mean teamwork scores were 6.6 (0.75) with a decrease to 6.53 (0.70) in Jan–Mar 2016.



Abstract 277 Figure 1

Most scores were assigned by a charge nurse (46.2%). Nurse Practitioners gave slightly lower scores when compared with other groups ($p<0.05$). There was little correlation between TIAEs and teamwork scores ($r=-0.082$).

Conclusions There was an expected decrease in teamwork scores with additional staff training. This finding has been previously described and results from more accurate evaluations. The increase in TIAE incidence in Oct–Dec 2015 could be due to a lower mean gestational age. We are continuing to implement the program with training expected to be complete by Dec 2016.

278 SURVEY OF VENTILATORY PRACTICES IN MANAGEMENT OF RESPIRATORY DISTRESS SYNDROME IN PRETERM INFANTS

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10.1136/jim-2016-000365.278

Purpose of Study To ascertain current practices in the ventilatory management of respiratory distress syndrome (RDS) in neonatal units in the United States.

Methods Used An online, survey-based questionnaire on ventilatory practices for management of RDS in the first hour of life was distributed to members of the Section on Neonatal Perinatal Medicine of the American Academy of Pediatrics. Sample size of 353 was calculated a priori for a confidence interval of 95% and margin of error of 5%.

Summary of Results Responses were received from 409 neonatologists practicing across 45 states. Sixty percent of respondents practiced in an academic center. In preterm infants less than 26 weeks, 31% of respondents would consider elective invasive mechanical ventilation and surfactant administration, while 26% reported performing intubation, surfactant and extubation (INSURE) procedure and continuing either nasal continuous positive airway pressure (NCPAP:15%) or nasal intermittent positive pressure ventilation (NIPPV:11%). Thirty-four percent of respondents would initiate NCPAP and 9% would consider NIPPV without prophylactic or early rescue surfactant. For preterm infants between 26 and 30 weeks, NCPAP was the most preferred mode of ventilation (70%; 12% after INSURE). Similarly, NCPAP was reported by majority of respondents (91%; 8% after INSURE) in preterm infants between 30 and 36 weeks gestation (table 1). The respondents report basing their practices on the following level of

Abstract 278 Table 1 Ventilatory modes based on gestational ages (n=409).

Gestational age	Elective intubation, Surfactant and IMV	INSURE and NIPPV	INSURE and NCPAP	NIPPV	NCPAP
Less than 26 weeks	31.3%	10.76%	15.16%	8.80%	33.99%
26–30 weeks	3.18%	11.00%	12.22%	15.65%	57.95%
30–36 weeks	0.49%	1.47%	8.07%	6.60%	83.37%

evidence: meta-analysis (29%), one or more randomized controlled trials (39%), physiologic rationale or personal experience (13%), while 10% reported lack of evidence.
Conclusions Ventilatory practices for early management of RDS were variable, especially in extremely premature infants born less than 26 weeks gestational age. NCPAP was the preferred mode of ventilation in more mature preterm infants. There is wide variation in the reported level of evidence on which these ventilatory practices are based.

279 PREDICTORS OF OUTCOMES AFTER SUCCESSFUL LESS INVASIVE POSITIVE PRESSURE SUPPORT DURING RESUSCITATION OF LARGER PRETERM AND TERM INFANTS IN THE DELIVERY ROOM

Wang ER,[1] Wertheimer FB,[2] Ramanathan R,[2] Biniwale M[2]. [1]*Keck School of Medicine of USC, Los Angeles, CA;* [2]*Keck School of Medicine of USC, LAC +USC Medical Center, and Children's Hospital of Los Angeles, Los Angeles, CA.*

10.1136/jim-2016-000365.279

Purpose of Study We compared outcomes after successful less invasive positive pressure support (LIPPS) using nasal intermittent positive pressure ventilation (NIPPV) and/or CPAP with infants who did not respond to LIPPS during neonatal resuscitation of larger preterm and term infants in the delivery room (DR) at our institution. Failure of LIPPS was defined as need for endotracheal intubation in the DR.
Methods Used Data on all infants with birth weight of ≥1500 g requiring LIPPS in the DR was prospectively collected in our neonatal intensive care unit database from 1/2009 to 12/2015. Institutional review board approval was obtained. Data from infants who received successful LIPPS was compared with data from infants intubated in DR after unsuccessful LIPPS. Maternal characteristics and comorbid conditions were studied. Outcomes included chest compressions, air leak syndrome, requirement of invasive ventilation at 24 hours, and death.
Summary of Results Out of 768 infants provided NIPPV and/or CPAP, 686 received successful LIPPS while 82 required intubation. We saw no significant difference in maternal characteristics between the two groups. Intubation rates were lower in infants receiving LIPPS (p=0.001). At 24 h of age, 58.2% of infants remained intubated in intubated group vs. 7.0% in successful LIPPS group (p<0.001). Nine infants in intubated group received chest compressions vs. 5 in successful LIPPS group (p<0.001). Air leak rates were similar in intubated and successful LIPPS groups (4.2% and 4.9%, respectively). Four infants in the intubated group expired compared to one in successful LIPPS group. Significantly more patients in the intubated group were diagnosed with RDS (p=0.01), meconium aspiration (p=0.014), HIE (p<0.001), and sepsis (p<0.001).
Conclusions Infants requiring DR intubation are at higher risk for mortality and morbidities compared to the infants responding to LIPPS. Successful DR LIPPS was associated with increased use of NIPPV and lower chest compression rates. Fewer infants remained intubated at 24 h with successful LIPPS. Lower rates of comorbidities were associated with successful LIPPS.

280 ELEVATED SERUM VITAMIN D LEVELS ASSOCIATED WITH NEPHROCALCINOSIS IN PRETERM INFANTS

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10.1136/jim-2016-000365.280

Purpose of Study Nephrocalcinosis (NC) is the calcification of renal tissue, and is found in 7–64% of preterm infants with gestational age (GA) <32 weeks or <1500 g. Hypercalciuria can cause precipitation and adherence of calcium crystals to the renal tubular epithelium leading to NC. NC risk factors, screening options, exact etiology and relationship among vitamin D metabolism, urinary calcium loss, and the effect on bone mineral density in preterm infants remains unknown.
Methods Used This is a prospective observational cohort study including 42 infants with GA ≤32 wks or BW ≤1800 g. Weekly urinalysis was started at 2 wks of age. The presence of NC was confirmed by renal ultrasound (US). Data were collected on demographics, dietary intakes, medications and serum vitamin D levels. Bone mineral density was assessed using total body dual energy X-ray absorptiometry (DXA) scan and tibial bone US at the time of discharge.
Summary of Results 20 (48%) of 42 infants were diagnosed with NC. NC infants were of lower GA (P <0.01) and BW (P<0.01). More males (15/20) than females (5/20) had NC (P=0.12). Postnatal steroid and furosemide therapy were higher in the NC group (P<0.05); but only GA and BW were significant risk factors by regression analysis. Urinary calcium oxalate crystals were found in 80% of NC infants versus 45% Non-NC, (P<0.03; PPV=62% & NPV=75%). There were no differences in daily dietary intakes for Ca, P, or Vit D between groups. Near discharge, serum 25-OH Vitamin D levels were higher in the NC group (48±6 ng/ml) compared to the Non-NC group (31 ±5 ng/ml) (P=0.03). Serum Ca level in the infants with NC was 10±0.07 mg/dL compared to 9.8±0.09 mg/dL in the NonNC infants (P=0.06). Tibial bone US demonstrated reduced bone elasticity and strength in the NC group (P<0.01).

Conclusions Infants born at earlier gestation and lower birthweight are at increased risk of NC. Urinalysis for the presence of calcium oxalate crystals may be an effective initial screening tool. Serum vitamin D levels were increased and the bone elasticity and strength was decreased in the infants with NC. We speculate the calcium deposited in the kidneys likely originates from the infants' bones resulting in diminished bone quality.

281 ACUTE KIDNEY INJURY (AKI) IN PRETERM INFANTS RECEIVING INDOMETHACIN FOR PATENT DUCTUS ARTERIOSUS (PDA)

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10.1136/jim-2016-000365.281

Purpose of Study Indomethacin, a commonly prescribed nonsteroidal anti-inflammatory drug (NSAID), is known to be highly nephrotoxic. Preterm infants receiving indomethacin may be at an increased risk of AKI. We investigated AKI incidence in indomethacin-exposed infants using a recent standardized definition, and determined the percentage of patients with adequate serum creatinine (SCr) monitoring required to sufficiently diagnose AKI.
Methods Used This retrospective study includes 70 preterm infants (≤34 weeks GA) who received indomethacin treatment for symptomatic (n=38) or prophylactic (n=32) treatment for PDA between Jan-Dec 2014 at BC Women's NICU. Indomethacin symptomatic dosing: 0.4–0.6 mg/kg divided over 36 hours at 0–3 weeks of life; prophylactic: 0.3 mg/kg divided over 72 hours at ≤24 hours of life. Available SCr and 12-hr urine output (U/O) were recorded from admission to 7 d post indomethacin exposure. AKI incidence was determined using modified Kidney Disease: Improving Global Outcomes (KDIGO) ΔSCr (50% rise from prior SCr within 7 d or 0.3 mg/dL rise within 48 hrs) & U/O (<1 cc/kg/hr, excluding the first 24 hrs of life).
Summary of Results In symptomatic group: 33/38 (87%) had available pre and post-treatment SCr values for adequate evaluation of AKI. Of these patients, 2/33 (6%) met ΔSCr AKI criteria. Incidence was 13/38 (34%) when including U/O criteria. In prophylactic group: 4/32 (13%) had adequate SCr monitoring; 1/4 (25%) met ΔSCr AKI. One additional patient achieved U/O criteria, totalling an overall AKI incidence of 2/32 (6%), which was lower than that of symptomatic treatment group (p=0.007).
Conclusions AKI incidence is higher in infants treated with indomethacin for PDA closure compared to those treated prophylactically during the first day of life. While this may be attributed to lower doses of indomethacin exposure in the prophylactic group, limitations with lack of SCr monitoring and the variable onset of U/O during the first day of life may inhibit accurate diagnosis in prophylactic patients. To improve AKI identification, standardized protocols for monitoring daily SCr and U/O around exposure should be implemented for all neonates with NSAID exposure.

Surgery III
Concurrent Session
8:00 AM – 10:00 AM
Friday, January 27, 2017

282 MITOCHONDRIAL ASSESSMENT OF REPERFUSED PORCINE LUNGS FOLLOWING COLD STATIC STORAGE

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10.1136/jim-2016-000365.282

Purpose of Study There is an ever-growing shortage of available organs for transplantation. One contributor is the 6–8 hour time frame lungs can currently be preserved. Better understanding the mitochondrial component of preservation may lead to innovations in whole organ preservation, increasing the number of usable organs for transplant. In our study we analyzed election transport chain (ECT) complexes as a measure of mitochondrial preservation of porcine lung after one hour of physiologic reperfusion with the TransMedics©, organ care system (OCS).
Methods Used Porcine lungs, (N=3 for each time point), were procured and flushed with low-potassium dextran solution (LPD), enriched with heparin solution. The lungs were submerged and stored in ice-cold (4C) LPD for 4, 10, and 16 hours, in alignment with conventional preservation standards. Lungs were sequentially reperfused under physiologic conditions in the OCS for one hour, using a mixture of packed porcine red blood cells and plasmlyte. Mitochondrial isolates were extracted from porcine lung base following reperfusion. ECT assays were performed using Seahorse XF^e 96 analyzer measuring oxygen consumption rates (OCR) to calculate mitochondrial respiration states.
Summary of Results The ETC assay measured relative complexes in the respirator chain. Complex I respiration in 16 hour samples compared to 4 hour samples showed a significant decrease in OCR. To determine the relative change in OCR, respiratory complex ratios were calculated per complex from the absolute OCR.16 hour preservation exhibited lower relative respiration in the I/IV complex ratio than the 4 hour group, (p<0.05;). There was no significant difference between 4 hour to 10 hour I/IV complex ratio group or the 10 hour and 16 hour I/IV complex ratio group.
Conclusions This study describes the effects of prolonged static storage on mitochondrial bioenergetics in porcine lung following one hour of physiologic reperfusion. The results suggest decreased complex I respiratory function as static storage time increases. Inadequate mitochondrial protection during storage in LPD may be a major limiting factor in extending ex vivo lung longevity.

283 MANAGEMENT OF LARGE WOUND DEFECTS WITH CONTINUOUS TISSUE EXPANDERS

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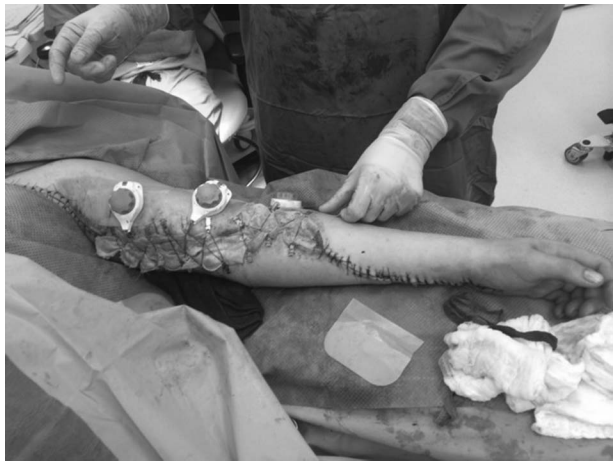
10.1136/jim-2016-000365.283

Purpose of Study Large wound defects often consist of areas with significant unapproximated skin edges. Typically,



Abstract 283 Figure 1 1. DermaClose post fasciotomy from rhabdomyolysis

complicated and labor-intensive techniques are employed to achieve primary closure. These methods include staged closure, full thickness skin grafts, and internal tissue expanders. Although these surgical interventions achieve excellent results, the elevated incidence of wound complications, unsatisfactory cosmesis, and high surgery costs favor the use of an alternative approach. In this study, we describe the utilization of a simple continuous external tissue expander, the DermaClose device, on eight patients to successfully manage large wound defects.

Methods Used Per each DermaClose device, 3 pairs of skin anchors were placed 2–3 cm apart and 2 cm from the wound edges. The Dermaclose device was applied per manufacturer's instructions. The device was removed after achieving adequate tissue expansion. Fasciocutaneous flaps were closed with interrupted PDS 2–0 sutures at the deep fascia level, and interrupted vertical mattress prolene 2–0 sutures for skin closure.

Summary of Results Complete primary closure of 9 large wound defects ranging from 1.8 cm×4.2 cm (width×-length) to 16 cm×35 cm was achieved. No incidents of dehiscence or major complications requiring reoperation were encountered.

Conclusions These results contribute to the growing body of literature demonstrating successful management of large wound defects through the use of continuous external tissue expanders. Recognition of the DermaClose device as durable medical equipment in federal and corporate medical policies will enable surgeons to utilize it on insured patients without the financial burden.

284 SURVIVORSHIP ANALYSIS OF MODULAR FEMORAL STEMS IN TOTAL HIP ARTHROPLASTY, MINIMUM 10 YEAR FOLLOW-UP

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10.1136/jim-2016-000365.284

Purpose of Study Total hip arthroplasty (THA) has historically relied on the use of non-modular femoral stems, while modular, multi-piece femoral stems were introduced in an effort to improve the anatomic matching and restore anatomic hip offset and leg length. Modular stems are advantageous when there is abnormal proximal femoral anatomy, significant bone loss exists, and they allow for potential improvements in gait and hip stability. Some noteworthy recent designs have had higher failure rates and recalls, thus currently limiting the use of modular hip stems. The senior author has used a unique modular stem design for over a decade, with good clinical results. Our study hypothesis is that the survivorship of this modular stem is similar to the survivorship of clinically successful non-modular femoral stems.

Methods Used We performed a retrospective implant survivorship analysis. The sample population consisted of all of the senior author's patients who received an OMNI Apex Modular 2nd generation implant from 2004 to 2006 (n=132), allowing us a minimum 10 year patient follow up. The survivorship endpoint was implant revision due to mechanical failure of the hardware. Multiple medical databases were searched and patients were contacted in cases where records were not sufficient, to determine survivorship.

Summary of Results Of the 132 patients, 4 were lost to follow up in the 10–12 year span. 17 more patients were excluded due to death before a 10-year post-op time was reached. However, none of the aforementioned 21 patients experienced a THA revision within their accessible medical records. Of the remaining 111 patients, 2 underwent revisions due to chronic infection in one case and metal on metal wear in the other. No patients experienced a mechanical failure of the implant; by commonly accepted standards this patient population had a 100% survivorship of their modular femoral stems at a minimum of 10 years post-op.

Conclusions The OMNI Apex Modular femoral implant has a equal or higher survivorship than competing non-modular stems on the market. We recognize that other studies have had longer retrospective timelines, but nonetheless this study shows hope for a new generation of modular stems. We conclude that modular femoral hip stems are not all associated with higher revision rates due to mechanical failure of the implant.

285 INNOVATION, ENGINEERING AND ANATOMY: PARADIGM SHIFT, ULTRASOUND ASSESSING IMPLANT POSITIONING, RESTORING THE HAND "ORGAN"

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10.1136/jim-2016-000365.285

Purpose of Study Upper-extremity injuries are the most common war injuries and highest rate leading to long-term disability in military personnel. Reconstructive tendon-transfer surgeries (TTS) have been utilized since World War II. Reports indicate 22% of hand surgeries performed in the military are TTS. The exemplar surgery used for this study, namely the TTS for median-ulnar nerve trauma, is one of the most common reconstructive TTS. Technology developed to advance this surgery will be available to military and civilian medicine. The objective is to develop implantable passive mechanisms for advancing surgery to

upper-extremity trauma and assessing it using ultrasound.
Methods Used Literature search was conducted on US assessing implant surgery to the hand. Deceased unembalmed donors (N=6 sides) received conventional TTS, Extensor Carpi Radialis Longus (ECRL)-Flexor Digitorum Profundus (FDP). Implants were designed, implemented into a 3D printer producing the plastic implant. Implant movement was assessed with ultrasound probes (5–12 & 18 MHz) and MRI scans. Each implant was examined and compared with ECRL and FDP tendons for size variation.
Summary of Results Literature search revealed no known studies. Surgical protocol was successful placing the implant. Implant moved unimpeded during tendon movements. Implants were placed and modified with each surgery-image session to improve differential movement of tendons distal to implant. This research is developing "new technology" facilitating optimal restoration post neuromuscular injury. The technology is applicable to other orthopedic surgeries of regenerative medicine, where implants are integrated with or constructed from tissue-engineered muscles and tendons. It promotes improved quality of life by an effective return to desired real-world activities. Fundamentally, it enables re-engineering of the human body through surgery and improves patient quality of life when compared with state of the art techniques. Real time ultrasound of the tendon movement with the implant in situ could confirm intraoperative success diminishing post-morbidity function.
Conclusions This multidiscipline study used a dissection lab to design, assess with ultrasound, and develop an implant for median-ulnar nerve injuries to restore natural function to the hand "organ".

286 MATCHED COMPARISON OF CONVENTIONAL FLUOROSCOPY, ULTRASOUND GUIDANCE AND THE LASER DIRECT ALIGNMENT RADIATION REDUCTION TECHNIQUE FOR PERCUTANEOUS NEPHROLITHOTOMY

Mattison BJ, Abourbih S, Keheila M, Yang P, Alsyouf M, Smith J, Baldwin D.
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10.1136/jim-2016-000365.286

Purpose of Study During percutaneous nephrolithotomy (PCNL), access is traditionally obtained fluoroscopically. Recently, ultrasound-guided (US) techniques requiring advanced sonographic skills have been described. In an attempt to combine the reduced radiation of US with the simplicity of fluoroscopy a modified technique combining fluoroscopy, a laser-guided C-arm, and direct endoscopic visualization, called the Laser Direct Alignment Radiation Reduction Technique (DARRT) was developed. The purpose of this study was to compare the safety and efficacy of the Laser DARRT technique to conventional and US-guided PCNL.
Methods Used Seventy-five PCNL patients, including the first 25 consecutive Laser DARRT, the first 25 consecutive US-guided and 25 conventional fluoroscopic patients matched for age, BMI, stone burden and location were reviewed and compared. Outcomes examined were total fluoroscopy time and access fluoroscopy time, stone-free rate, operative time, estimated blood loss, and major complications. Statistical analysis was performed using Kruskal-Wallis Test for continuous and the chi-square test for categorical variables.
Summary of Results Baseline demographics and mean stone burden were similar between groups. Median access fluoroscopy time was 3.1, 840 and 8.9 seconds, and total fluoroscopy time was 8.5, 940 and 17.4 seconds for US, conventional, and laser DARRT PCNL respectively. Both US and DARRT had significantly lower total and access fluoroscopy times than conventional PCNL ($p<0.01$), and there was no difference between US and laser DARRT ($p>0.05$). Stone-free rates between the US (68%), conventional PCNL (77%) and laser DARRT (84%) were similar ($p=0.27$). Major complications and EBL were not significantly different between the groups. Operative time for the laser DARRT was 20 minutes shorter than the conventional PCNL and 24 minutes shorter than the US. However, this difference did not reach significance.
Conclusions The Laser DARRT technique resulted in favorable operative times and stone free rates compared to both conventional and US-guided PCNL, and a 98% reduction in total fluoroscopy time compared to conventional PCNL.

287 PEDIATRIC PATIENTS WITH COCHLEAR IMPLANTS: OBSTACLES TO FULL-TIME UTILIZATION

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10.1136/jim-2016-000365.287

Purpose of Study The majority of children with cochlear implants (CI) are full time users. However, some choose to either use it occasionally or to discontinue use despite being considered appropriate candidates for implantation. The factors leading to this decision are not well understood. The aim of this study was to determine the proportion and characteristics of pediatric cochlear implant patients who are currently partial or non-users, as well as the reasons behind less than full-time use.
Methods Used To identify partial or non-users, audiology and medical records were reviewed for patients who had received a cochlear implant at BC Children's Hospital (BCCH) between January 1, 1989 and May 31, 2016, and were under 18 years of age as of June 30, 2016. A follow up telephone survey was completed with this population to determine actual hours of CI use and barriers to full-time use.
Summary of Results Charts of 150 patients were reviewed and 35 patients were identified as either partial or non-users. Thirty families were subsequently interviewed (86% response rate). Of these, 23 patients had unilateral CI and 7 had bilateral CIs. Of the unilateral CI patients, 15 were part-time users, 3 were non-users, and the remaining 5 patients reported that they were currently full-time users, indicating our screening via chart review was imperfect. Among the bilateral CI patients, 6 patients used one CI full-time and were either a partial or non-user of the other, and 1 was a non-user of both CIs. Main reasons reported for decreased/non use were fatigue from the effort of listening, loudness intolerance, magnet irritation, autism and complex medical conditions, physical barriers, lack of support services at

school and for speech-language therapy, parents' desire for children to be part of the Deaf/American Sign Language community, and perceived lack of benefit.

Conclusions A small but significant (25/150; 16.7%) portion of BCCH pediatric cochlear implant patients are less than full-time users of their CIs. There was a wide range of stated reasons, from physical barriers to psychosocial factors to the lack of support services in the community. These findings suggest closer follow up of this population is required.

288 SRC IS PART OF THE MECHANOTRANSDUCTION RESPONSE TO STIFF MATRIX IN PRIMARY HEPATOCYTES

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10.1136/jim-2016-000365.288

Purpose of Study In the progression of end stage liver disease, the liver becomes increasingly fibrotic and unable to repair itself. Injured hepatocytes are replaced by extracellular matrix (ECM). Transplantation is the only treatment, but the shortage of donor organs is a major limitation. Liver tissue engineering may be an alternate way to meet this need for donor livers. Unfortunately, the current reliance on rigid scaffolding to generate solid tissues alters cellular organization and ECM deposition. Our lab previously determined that stiffened matrix in fibrotic livers directly inhibited hepatocyte function (Desai *et al.*, Hepatology, 2016).

The purpose of this study is to investigate the signaling pathways involved in the hepatocyte response to rigid ECM. In particular, focal adhesion kinase (FAK), involved in the integrin cascade, is examined to ascertain its effect on other fibrotic regulators, including Signal transducer and activator of transcription 3 (Stat3), which promotes liver fibrosis through the actions of transforming growth factor β, and Proto-oncogene tyrosine-protein kinase Src (Src), which has a signaling role downstream of focal adhesions.

Methods Used Primary mouse hepatocytes were isolated from wild-type and FAK-deficient mice and cultured on collagen-conjugated polyacrylamide gels using a bis cross-linker to create a range of matrix stiffness. Protein quantifications for phospho-FAK, phosho-Stat3, and phospho-Src were then compared to total expressed protein levels.

Summary of Results Phospho-Src exhibited increased expression in hepatocytes cultured on 1 kPa (fibrotic liver stiffness) and 60 kPa (supra-physiological stiffness) gels compared to that of 140 Pa (normal liver stiffness) gels. Expression of phospho-Src was lower in FAK-deficient hepatocytes than the wild-type, while phospho-Stat3 was increased in FAK-deficient hepatocytes when measured against the wild-type.

Conclusions Phospho-Src increased with matrix rigidity but decreased in the absence of FAK, suggesting that Src is activated by greater matrix stiffness and cross-regulated by FAK. The upregulation of phospho-Stat3 in FAK-deficient hepatocytes suggests that the JAK-STAT pathway may play a compensatory role in the response to matrix rigidity when FAK is not present.

289 DUAL CATHETER HEMOSTATIC SANDWICH TECHNIQUE FOR CONTROL OF TRACT HEMORRHAGE FOLLOWING PERCUTANEOUS NEPHROLITHOTOMY

Mattison BJ, Keheila M, Kelly I, Abourbih S, Lightfoot M, Li R, Alsyouf M, Myklak K, Baldwin D. *Loma Linda University School of Medicine, Loma Linda, CA.*

10.1136/jim-2016-000365.289

Purpose of Study During percutaneous nephrolithotomy (PCNL), bleeding may arise from the percutaneous tract. We have previously described a technique to control percutaneous tract hemorrhage using a dual-nephrostomy gelatin matrix hemostatic sealant (GMHS) sandwich. The purpose of this study is to review the safety, efficacy, and clinical outcomes of this technique in a series of patients.

Methods Used A single institution, retrospective review of 304 PCNL procedures was performed. The clinical and perioperative characteristics of patients receiving the dual catheter hemostatic sandwich technique either with or without GMHS were reviewed. In the hemostatic sandwich technique, a 22 Fr Council-tip catheter is placed through the nephrostomy tract at completion of PCNL and the balloon is inflated just inside the nephrostomy tract. A second 16 Fr Council-tip catheter is placed with the balloon located just beneath the skin. GMHS is injected between the two catheters and then the second balloon is inflated. This technique was performed only in cases with moderate or severe persistent tract bleeding failing conservative measures including manual compression (10 minutes). For cases of moderate tract bleeding, GMHS was omitted in select patients to minimize cost.

Summary of Results Of 304 PCNLs, 27 patients received the dual catheter hemostatic technique (24 with and 3 without GMHS). The mean operative time was 197 minutes, with 3 patients requiring early termination of the operation due to bleeding and mean EBL was 254 cc. Transfusion of two units of blood was required in each of 2 (7.4%) patients. For patients who received the dual catheter hemostatic technique the hemoglobin stabilized at an average of 2.14 days. There were no complications related to the application of GMHS.

Conclusions The dual catheter hemostatic sandwich technique effectively controls tract bleeding following PCNL and may reduce the risk of delayed hemorrhage. There were no cases of delayed bleeding, allergic reactions, ureteral obstruction or any other complications related to the technique. The dual catheter hemostatic technique should be considered in cases of moderate or significant tract bleeding.

Behavior and Development I
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

290 NONWORD REPETITION SKILLS OF YOUNG CHILDREN BORN PRETERM

Gresch LD,[1] Loi EC,[1] Ashland M,[2] Marchman VA,[2] Feldman HM[1]. *[1]Stanford University, Stanford, CA; [2]Stanford University, Stanford, CA.*

10.1136/jim-2016-000365.290

Purpose of Study Nonword repetition (NWR) is a task that requires children to repeat pronounceable nonwords

and has been suggested as a tool for identifying children with language impairment (LI). The goal of this study was to expand understanding of language development in children born preterm (PT) by comparing their NWR performance to that of children born full term (FT) and exploring the underlying speech skills that may contribute to their performance.

Methods Used A NWR task was administered to 36-mos-old children born PT (N=60) and FT (N= 49). Children were asked to repeat 1- to 5-syllable nonwords. Responses were transcribed from recordings and scored using 2 measures of accuracy of speech sound production: Percentage of Consonants Correct (PCC) (completely accurate sound productions scored as correct) and an adapted version of PCC-Revised (PCC-R) (sound distortions and age-appropriate substitutions also scored as correct). Data were analyzed to determine birth group differences in NWR and differences in performance based on scoring method.

Summary of Results Children born PT scored significantly below children born FT using both PCC (PT M=.55, FT M=.61), t (107)=−2.07, p=0.04 and PCC-R (PT M=.71, FT M=.76), t (107)=−2.00, p=0.05. As expected, there was a significant main effect of nonword length on PCC scores, F (2, 101)=269.00, p<0.001. However, the group by length interaction failed to reach significance, p=0.26. A similar pattern was found using PCC-R scores. Scores for both groups were significantly higher with the relaxed PCC-R scoring (PT M=.71, FT M=.76), compared to PCC scoring (PT M=.55, FT M=.61), F (1, 107)=268.95, p<0.001, but there was no group by scoring method interaction, p=0.73.

Conclusions While children born PT scored below their FT peers on a test of NWR, their pattern of performance did not significantly differ from that of their FT peers. Similar to findings with other clinical populations, NWR holds promise for identifying children born PT who are at risk for LI. Because deficits in oral language are implicated in children with academic challenges, including reading disorders, future research should consider identifying factors associated with NWR that may be amenable to intervention.

291 DEVELOPMENTAL DIFFERENCES IN THE EARLY STAGES OF LEARNING TO READ IN CHILDREN BORN PRETERM AND FULL TERM

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10.1136/jim-2016-000365.291

Purpose of Study Reading has become a critical skill for academic and occupational success. Yet, about 10% of school children have a reading disability (RD), defined as deficits in decoding, comprehension, or both. Most research on RD has focused on typically developing, otherwise healthy children. Approximately 10% of children in the US are born preterm (PT) and are at elevated risk for poor reading compared to their full term (FT) peers. The primary objective of this study was to describe differences in reading abilities between birth groups in the early stages of learning to read.

Methods Used This longitudinal cohort study examined the development of reading skills in children born PT (n=36) and FT (n=32). Children were assessed using standardized tests of intelligence, language, phonological awareness, and reading from ages 6–8 years old. The primary outcome at age 8 was the GORT Oral Reading Index (ORI), a composite of fluency (rate and accuracy) and comprehension scaled scores.

Summary of Results The proportion of children who were unable to decode pseudowords at age 6 was higher in the PT group than the FT group (55% vs 31%, chi-square=4.1, p=0.04) despite a higher rate of family risk in the FT children (3% vs 25%, chi-square=7.3, p=0.008). Hierarchical multiple regressions were run to determine if the addition of decoding efficiency (TOWRE-2) and passage comprehension (WRMT-III) predicted reading at 8 over and above socioeconomic status (SES), nonverbal IQ (PIQ) and family risk at age 6. The model was significant for predicting reading skills from PIQ and SES in the PT, but not the FT group ($R^2\Delta$=0.55, p=0.001). The addition of family risk, dyslexia, or difficulty spelling significantly increased the variance accounted for in both groups (PT $R^2\Delta$=0.10, p=0.005; FT $R^2\Delta$=0.19, p=0.011). Finally, the TOWRE-2 and WRMT-III increased the overall model fit in both PT and FT children (PT $R^2\Delta$=0.09, p=0.014; FT $R^2\Delta$=0.44, p=0.001), although it accounted for over 4 times the variance in the FT than PT children.

Conclusions Patterns of predictors are different in PT and FT children. Decoding and comprehension at age 6 predicted reading abilities at age 8 in both groups. Early interventions to enhance these skills should be pursued to improve reading abilities.

292 PRENATAL INFECTIONS AND RISK OF AUTISM, INTELLECTUAL DISABILITY AND/OR EPILEPSY

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10.1136/jim-2016-000365.292

Purpose of Study Although studies have reported associations between infections and febrile episodes in pregnancy and autism and intellectual disability (ID) in offspring, results are mixed and limited to specific populations. We examined the association between maternal inpatient diagnosis of infection and childhood risk of autism, ID and epilepsy in a population-based birth cohort.

Methods Used This retrospective study included California singleton births from 1/1/1991–12/31/2008 that survived the first year of life (n=8,618,171). Infection during pregnancy was defined using ICD-9-CM codes from any maternal hospitalization. Birth files were merged with records from the California Department of Developmental Services (DDS) for children receiving care from 1/1/1991–12/31/2012, identifying 42,998 with autism, 45,546 with ID and 2,507 with epilepsy. Outcomes were defined by the DDS using standardized assessments and ICD-9-CM codes. Multinomial logistic regression models calculated relative risks and 95% confidence intervals for autism, ID or epilepsy in children according to maternal infection status, controlling for maternal age, race/ethnicity, educational attainment, payer, parity and birth year. Additional models using sub-

categories of the predictor explored the effect of type, site, fever propensity and timing on outcomes of interest.
Summary of Results Maternal infection was associated with an increased risk for autism (8%), ID (33%) and epilepsy (43%) in adjusted analyses. Febrile infections elevated risk in a similar manner. Stronger associations were observed between infection sub-categories and ID and epilepsy, including bacterial etiology (increased by 43% and 57%, respectively) and respiratory (29% and 38%, respectively) and genitourinary (39% and 48%, respectively) sites. Outcome risk differed by timing of infection, with second trimester infections conferring a 24% increased risk for autism and a greater than two-fold risk for ID and epilepsy, and third trimester timing elevating risk to a lesser degree.
Conclusions This study adds to the growing body of evidence implicating immune-mediated exposures during fetal development in the etiology of autism, ID and epilepsy. The second trimester appears to represent a critical window of susceptibility during wch maternal infection can disrupt core mechanisms involved in fetal neurodevelopment.

293 IMPACT OF CHRONIC MEDICAL CONDITIONS ON ACADEMICS OF CHILDREN IN THE CHILD WELFARE SYSTEM

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10.1136/jim-2016-000365.293

Purpose of Study National Survey of Child and Adolescent Well-Being (NSCAW I) is the 1st nationally representative, longitudinal study of children (0–14 y, N=5501) involved in child welfare system (CWS) investigations. Aims: (1) To determine if chronic medical conditions contribute to academics and (2) To identify factors associated with better academics. Hypothesis: Children with non-CNS conditions of interest (COI) have better academic achievement than children without chronic conditions (NONE) and children with all other chronic conditions, including CNS involvement (OTH). COI could be associated with better outcomes if frequent medical system contact confers protection in other life aspects. Or, similar to the general population, there could be added negative impact of chronic medical conditions.
Methods Used Secondary data analysis of Waves 1 (baseline) and 4 (36 months post baseline). Parent reported on 24 chronic conditions; children were divided into 3 groups: COI (asthma, eczema, allergy, diabetes), OTH (all other chronic conditions), NONE. Using NSCAW sampling weights, hierarchical logistic regression models addressed factors associated with better academics. Predictor variables: chronic condition group, sex, income level, case substantiation, placement, and school engagement. Covariate: IQ. Outcome variables: Better performance for reading and math achievement (Woodcock std score ≥85).
Summary of Results In the TOTAL group, 80% had better reading; more in the COI (85%) vs NONE (79%) and OTH (80%), adjusted F=433, p<0.001. In the TOTAL group, 67% had better math; more in the NONE (68%) and COI (68%) vs OTH (60%), adjusted F=1278, p<0.001. Models predicting to better reading and math achievement were significant, with R^2=0.51, p<0.001 and R^2=.43, p<0.001. COI had increased odds of better reading achievement (OR 1.3, 95% CI 1.3–1.4). Both COI and OTH had lower odds of better math achievement (OR 0.87 and 0.76), p<0.001. Male sex and poor school engagement had lower odds of better reading (OR 0.44 and 0.85) and math achievement (OR 0.62 and 0.49), all p<0.001.
Conclusions Children in CWS are generally at high risk for poor outcomes. Our results suggest that increased contact with the medical system may provide an opportunity for better reading achievement. We recommend increased surveillance and referral for educational and behavioral services and supports.

294 SUBSTANCE USE DISORDER AND CONDUCT DISORDER IN ADOLESCENCE PREDICT MEDICAL CANNABIS CARD STATUS IN ADULTHOOD

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10.1136/jim-2016-000365.294

Purpose of Study To examine if a substance use disorder (SUD) and/or conduct disorder (CD) diagnosis in adolescence predicts future medical cannabis card status.
Methods Used Data collection occurred in Denver and San Diego. We recruited adolescents, 14–18 years of age, with or at high risk for SUD (hereafter probands) and their siblings (N=665). Baseline (Wave 1) assessments took place between 1999 and 2008, and follow-up (Wave 2) assessments took place between 2010 and 2013. The mean age at Wave 1 was 17.3 years (SD=3.1) and at Wave 2 it was 24.1 years (SD=2.5).

Wave 1 predictors selected *a priori* included: (1) baseline age, (2) time between Wave 1 and 2 assessments, (3) sex, (4) substance abuse or dependence diagnoses, (5) number of cannabis abuse or dependence symptoms, (6) number of non-cannabis substance use disorder diagnoses (range 0–8), (7) CD, (8) generalized anxiety disorder, (9) major depressive disorder and (10) attention-deficit/hyperactivity disorder (ADHD). Wave 1 endorsement of cannabis dependence criterion A7 (i.e. using cannabis despite a physical or psychological problem that is likely to have been caused or exacerbated by cannabis use) was also tested.

Bivariate analyses were conducted based on outcome of interest: medical cannabis card status at Wave 2. For categorical predictor variables chi-square statistics were utilized. For continuous variables, t-test was utilized to compare groups (or Mann Whitney U tests when normality could not be assured).
Summary of Results Of the Wave 1 predictors tested, the following significantly predicted Wave 2 medical cannabis card status: male sex, proband status, a tobacco, cannabis, amphetamine, or hallucinogen SUD, a higher number of cannabis SUD symptoms, number of non-cannabis SUDs, endorsement of criterion A7, and a CD or ADHD diagnosis.
Conclusions Cannabis SUD and CD, among other variables in adolescence positively predicted future medical cannabis card holder status. Future cannabis policies should consider high-risk adolescent populations as they may be more impacted than the general population. In the future, a full model controlling for site, relationship (proband, sibling) and family will be built to ensure that predictor-to-card-status relationships remain significant.

Global Health II
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

295 DIABETIC FOOT AMPUTATION IN SOROTI, UGANDA – THE PATIENT PERSPECTIVE

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10.1136/jim-2016-000365.295

Purpose of Study In Uganda, the increase in non-communicable diseases (NCDs) such as type 2 diabetes presents a significant burden to health care. Despite this, little attention has been given to diabetic sequelae or their impact. In recent years, surgeons in Soroti, Uganda noticed an increased frequency of Diabetic Foot Amputations (DFA). The objective of this study was to assess the characteristics of patients with Type 2 diabetes undergoing DFA and the impact of DFA on their life.

Methods Used A mixed methods study was conducted from May-July, 2016 at Soroti Regional Referral Hospital (SRRH) in Teso region, Uganda. We performed a 40-month retrospective review of surgical theater records to document the proportion of DFA amongst lower extremity amputations (LEA) performed at SRRH. We then prospectively interviewed—in a semi-structured format—DFA patients presenting to the diabetic outpatient clinic, in order to document the demographic characteristics of the patient population, their management and the participants' perspective on their disease. Qualitative data were analyzed by inductive coding.

Summary of Results Diabetic Foot Amputation was the most common LEA at SSRH from January 2013 to June 2016 (25 DFAs or 28.7% of LEAs). The 21 DFA patients interviewed were predominately subsistence farmers; the mean age was 57.3 years (SD=12.7). Within 6 months prior to DFA, 71% of patients first presented to healthcare services with foot complications, while 33% received their initial diabetes diagnosis. By restricting the patient's ability to work, DFA presented substantial economic burden on the household. Transport and availability of medication were identified by the patients as the major barriers to accessing care.

Conclusions With the rising prevalence of diabetes in Uganda, ensuring early diagnosis is paramount if severe and irreversible sequelae are to be prevented. Community-based screening, patient education, and supply chain inadequacies offer targets for future interventions to reduce the disability and economic burdens of severe diabetes complications.

296 TACKLING MALNUTRITION AND ANEMIA IN THE SACRED VALLEY OF PERU

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10.1136/jim-2016-000365.296

Purpose of Study Ayni Wasi, an NGO based in Ollantaytambo, Peru, has identified that 60% of children in the Sacred Valley are stunted, and around 54% of those under 5 years of age have iron deficiency anemia. These communities at 9100–12500 ft of altitude face limited food availability and diversity. The objective of this project was to conduct micronutrient and economic analyses to improve Ayni Wasi's nutrition program and train health "promotoras" on the most nutrient dense and affordable foods available.

Methods Used More than 40 hours were spent in the markets in Ollantaytambo and Urabomba to obtain the prices of locally available foods. A micronutrient analysis was conducted using the USDA Food Composition Database, and a spreadsheet was made with the prices and content of iron, zinc, folate, vitamins A and C, protein, carbohydrates, fats, and calories. Using the NIH Health Professional Dietary Reference Intakes (DRIs), a picture-based presentation for low-literacy promotoras was made on the quantity of each food needed to obtain the DRI for each nutrient for children up to age of 8. A "my plate" picture-based diagram for anemia prevention was also designed.

Summary of Results An educational presentation on the "top 10" foods with each micronutrient, such as sweet potatoes and spinach for vitamin A, and their benefits was given to Ayni Wasi staff. These 9 individuals will teach the 6 docentes (advanced promotoras hired on staff), who will then teach the 55 health promotoras to bring the curriculum to their communities. Recipes, such as lentil and sweet potato stew, were designed with the Peruvian staff and a sample meal was prepared for a docente training day. Ayni Wasi staff and interviewed promotoras were enthusiastic to have resources to make more appropriate food recommendations and were convinced that over time the communities would make changes in their diets based on this new information.

Conclusions The project gave Ayni Wasi the knowledge and resources to recommend local foods that can, over time, impact the high rates of anemia and stunting. This knowledge will be sustainable over time once the promotoras have been trained during the scheduled nutrition training session in January. Subsequent to this training, Ayni Wasi will begin retesting the children previously diagnosed with anemia and the promotoras will be retrained every 6 months.

297 DECREASING TOBACCO SMOKING IN DHULIKHEL, NEPAL THROUGH CESSATION COUNSELING AND EDUCATIONAL PROGRAMS

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10.1136/jim-2016-000365.297

Purpose of Study The four most common causes of death in Nepal are all associated with smoking. Furthermore, in Dhulikhel, over a quarter of male adults are current smokers, and over a third of college students have smoked. Despite this high smoking rate and the mortality associated with it, there were no organized public health efforts against smoking at Dhulikhel Hospital. Therefore, the goal

of this project was to start sustainable antismoking programs.

Methods Used To determine which interventions would be most helpful in Dhulikhel, a literature review on tobacco smoking campaigns in developing countries was preformed and two qualitative surveys were conducted. One survey was administered to physicians at Dhulikhel Hospital, the other to a cross-section of the community. Based on feedback from these surveys, information form the World Health Organization was adapted for use in Dhulikhel and refined from further participant input as the programs proceeded. A thirty minute smoking cessation counseling protocol was developed and piloted by nurse educators at Dhulikhel Hospital. Also, two forms of an hour-long presentation on tobacco smoking, one for schools and one for community outreach events, were created and taught to Dhulikhel Hospital community health workers.

Summary of Results For over 4 weeks, inpatient smoking cessation counseling was offered twice a week and outpatient counseling once a week. Typically 3–5 patients were counseled each day, with a maximum of 12 per session, for a total of around 50 people counseled. All patients interested in stopping made concrete smoking quit plans, and believed the class was helpful. In addition, 5 informational classes were given to teenage students at three different schools near Dhulikhel. In total around 200 students attended. Nurse educators in Dhulikhel will continue to counsel patients using this curriculum, and community health workers will use their curriculum to teach more informational classes to schools and during community outreach events.

Conclusions Patients at Dhulikhel Hospital now have a tool to assist in their smoking cessation and hundreds of teenage students were provided smoking education. The Dhulikhel Hospital community health department plans to hire a full-time employee to promote smoking cessation using these curricula and other tools provided as a foundation for future work.

298 MIXED-METHODS COMPARISON OF FAMILY PLANNING MODELS

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10.1136/jim-2016-000365.298

Purpose of Study The World Health Organization cites family planning (FP) as an essential component of female autonomy and maternal health. This study evaluated two FP models used by community members in rural Nakaseke, Uganda: (i) a central outpatient clinic and (ii) community-based delivery of services by Community Health Workers (CHWs). It compared the models in regards to efficacy and client satisfaction in order to inform about the strengths and weaknesses of each model.

Methods Used Clinic clients (18) were recruited via radio broadcast and CHW clients (37) were contacted through client lists. Both males (1) and females (54) were included. A verbal survey, adapted from the Demographic and Health Survey FP Client Exit Interview, was administered to participants to compare client satisfaction and knowledge about FP. Post-survey, 17 Clinic clients and 17 CHW clients participated in focus groups, which explored common attitudes surrounding FP. The survey and focus groups were conducted with the aid of translators.

Summary of Results 97.2% of CHW clients correctly answered knowledge based questions regarding FP compared to 76.5% of Clinic clients (P=0.94). Additionally, 100% of CHW clients were "very satisfied" with their FP compared to 83.3% of Clinic clients (P=0.93). Focus group data showed that both groups used FP primarily for child spacing. Both cited stigma from their husbands and cultural myths as barriers to accessing FP. Key positives expressed by FP clinic clients were: variety of FP options and onsite physician access while CHW clients cited anonymity, personal connection and convenience as highlights. Conversely, clinic clients disliked the short opening hours and lack of privacy in the clinic while CHW clients identified the lack of certain FP options and limited CHW training as key negatives.

Conclusions This data suggests that there is no statistical difference in efficacy or client satisfaction between clinic and CHW FP delivery. Each model has its own strengths and weaknesses. CHW delivery of FP may be a successful alternative for women distal to clinic locations, for those in search of anonymity and can potentially be expanded to other health care services.

299 FORMING FIRST-AID HEALTH BRIGADES IN A PERUVIAN SHANTYTOWN SCHOOL

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10.1136/jim-2016-000365.299

Purpose of Study Puente Piedra is located in a poor, northern province of Lima that is comprised of slum zones, undeveloped areas, and pueblos jóvenes. Pueblo jóvenes are rural, low-income settlements where the community develops infrastructure and services as needed. Colegio Pitágoras educates 2,000 students and is set in this environment. As such, there is insufficient infrastructure, including: inadequate lighting, ventilation, temperature control, and safety measures to protect students from injury. Dehydration, heat stroke, hypothermia, and injuries from falls or fainting are common. The only health clinic is 12.5 miles from the school and there are no emergency health services. Due to the high incidence of injury-related disability and lack of emergency medical services, the aim of this project was to improve health outcomes by forming first-aid health brigades.

Methods Used Training materials were developed in collaboration with a local physician using resources from the Red Cross. Training included case studies, demonstrations, videos, and exercises to practice skills. Six students from each grade 4–8 interested in health education, 4 health professors, and 4 parents completed the training. All participants were given a First-Aid Guide developed specifically for the school that included twelve topics. Eight topics were chosen by Pitágoras faculty as the most relevant to include in

the training. Evaluations were distributed at the end of each training class to gauge the quality of the course and teacher, and to ascertain the knowledge and skills gained.

Summary of Results A total of 32 people were trained on first-aid topics. Post-training evaluations revealed that 83% of participants strongly agreed they had acquired new skills they identified as useful, 72% strongly agreed they could identify a sick dog and tell when a bite needed medical attention, 94% strongly agreed they felt comfortable performing the Heimlich Maneuver in an emergency, and 94% agreed they could treat a strain and sprain. Moreover, 61% rated the course as exceptional while 39% as satisfactory.

Conclusions The project trained a first-aid brigade equipped in best practices. Post-training evaluations revealed that basic first-aid skills were attained and the course was appreciated. Additionally, a professor was given a copy of the training materials in order to sustain bi-annual training.

300 THE ASSESSMENT AND SUSTAINABLE MANAGEMENT OF SICKLE CELL DISEASE IN THE INDIGENOUS THARU POPULATION OF NEPAL

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10.1136/jim-2016-000365.300

Purpose of Study In countries with endemic malaria, Sickle Cell Disease (SCD) is a well-documented, non-communicable cause of morbidity and mortality for reasons including splenic infarction and vasoocclusive crisis. Current research has shown that early diagnosis and intervention reduce negative outcomes of SCD. Our goal was to establish the prevalence of SCD and identify health disparities in the rural district of Dang, Nepal, where a high incidence of the disease has been suspected amongst the indigenous Tharu community.

Methods Used Between July 2015 and June 2016, a total of 2,899 Tharu patients were screened for SCD using the Sickledex screening test. Those who screened positive were offered gel electrophoresis diagnostic testing. Semi-structured qualitative interviews were conducted with a subsample of patients who screened positive (n=45) for the purpose of project evaluation, quality improvement, and assessing knowledge regarding SCD.

Summary of Results Out of 2,899 individuals, 271 screened positive, suggesting a 9.3% prevalence of sickle cell trait. After diagnostic testing (n=130, 48%), 6 patients were diagnosed with homozygous SCD. 141 out of the 271 patients with positive screens are waiting for diagnostic testing. Themes that emerged from the interview analysis include confusion between the screening and diagnostic tests, barriers to accessing care, and limited knowledge about SCD. For example, some of the patients believed that SCD was communicable and therefore avoided sharing food and water. In assessing health barriers, economic limitations and geographical isolation from tertiary care were a primary concern.

Conclusions This ongoing project creates an opportunity for simple yet high yield interventions to target issues around SCD in the low income setting. Future directions include working to develop nationwide screening at infancy in high risk populations, increasing accessibility of diagnostic gel electrophoresis testing, and continuing to educate members of the community about SCD etiology, diagnosis, and treatment.

301 HEALTH OUTCOMES OF LOW BIRTH WEIGHT INFANTS FOLLOWING IMPLEMENTATION OF A HOSPITAL-TO-COMMUNITY IN-HOME SURVEILLANCE INTERVENTION IN RURAL GUJARAT, INDIA: AN INTERIM ANALYSIS

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10.1136/jim-2016-000365.301

Purpose of Study Determine health outcomes following implementation of a structured surveillance program focused on survival and growth of LBW children through interventions during and after hospital delivery.

Methods Used This prospective cohort study took place at Mota Fofalia Pediatric Center (MFPC) in Gujarat, India. 1) A baseline pre-intervention assessment of growth status was done in a randomly selected cohort of LBW infants born between 01/2012–05/2014. 2) Starting in 08/2014, a community in-home surveillance intervention was implemented for all LBW infants born at MFPC. Trained community health workers performed pre-discharge counseling and post-discharge health evaluations through household visits based on WHO recommendations. Weight for age z-scores (WFAZ) were calculated using the WHO AnthroPlus software.

Summary of Results 120 LBW children were included for pre-intervention assessment: 62% female, mean birth weight (MBW) 2124 g (500 g–2500 g), median age at follow up 18 mo (1–28 mo). 24/120 (20%) had died. Among the 96 live children, 35/96 (36%) were moderately underweight (MU – WFAZ –2 to –3) and 28/96 (29%) were severely underweight (SU – WFAZ >–3).

417 LBW children were included for post-intervention assessment: 52% female, MBW 2190 g (510–2500 g), median age at follow up 11.7 mo (1–28 mo). 17/417 (4%) had died; 72 were lost to follow-up. Among the remaining 328 children, 126/328 (38%) were MU and 88/328 (27%) were SU.

Conclusions In an interim analysis, implementation of a structured hospital discharge procedure combined with an in-home surveillance program designed for trained community health workers was associated with improved survival. Growth outcomes in LBW infants were similar.

302 STRENGTHENING THE LOCAL HEALTH AND SOCIAL SAFETY NET OF FEMALE SEX WORKERS IN NAIVASHA, KENYA

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10.1136/jim-2016-000365.302

Purpose of Study There are an estimated 2,500 female sex workers (FSW) living in Naivasha, Kenya and the surrounding area. They are at increased risk for sexually

transmitted infections (STIs) including HIV, violence (emotional, physical, and sexual) and associated physical and psychological effects, late presentation of preventable or treatable diseases, unintended pregnancies, and post-abortion complications. They are less likely to access healthcare due to community stigma against their profession.

Methods Used The Naivasha Drop-In-Center (DIC) provides healthcare services for local FSW. Through DIC staff interviews, institutional data review and discussions with FSW, three top health priorities were determined for the Naivasha FSW population: enhanced response to violence (including violence prevention), HIV/STI prevention and access to treatment, and enhanced patient follow-up. Interventions to address these priorities included: development of formal referral systems between the DIC and two new partners, the Naivasha Hospital Continuing Care Clinic (CCC) and Agatha Amani House (AAH), a local women's shelter; medically accurate, targeted educational brochures; and a protocol for appointment reminders/patient follow-up via SMS.

Summary of Results Five brochures were developed in Kiswahili and are currently being used at biweekly DIC outreach events. Both new referral systems were formalized through signing a standard operating procedure (SOP) between the DIC both the CCC and AAH. Updated follow-up protocol (SMS and appointment cards) has been implemented for all patients since mid-August 2016. A presentation of these results was delivered to all Naivasha District Hospital staff in order to increase sensitivity toward and awareness of healthcare issues faced by FSW.

Conclusions The project identified weaknesses in healthcare delivery for FSW, a particularly vulnerable population, and utilized various evidence-based interventions to strengthen community capacity to meet the needs of FSW in a more sophisticated way. These interventions are self-sustaining due to joint development with DIC staff, but should be strengthened through increased partnerships with non-traditional partners (law enforcement and religious leaders) whose attitudes toward FSW contribute to stigma.

Health Care Research II
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

303 OUTPATIENT BURN CARE AT BC CHILDREN'S HOSPITAL BURN TREATMENT ROOM: A 3-YEAR REVIEW

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10.1136/jim-2016-000365.303

Purpose of Study The Burn Treatment Room (BTR) at BC Children's Hospital (BCCH) is run by a multi-disciplinary team, providing sedation to burn patients undergoing dressing changes in a monitored setting. The purpose of this study is to review the safety and efficacy of the BCCH BTR in conjunction with a qualitative analysis of staff experience.

Methods Used A retrospective chart review of all patients treated in the BTR from 2013 to 2015 was conducted as well as qualitative interviews with BTR staff.

Summary of Results 59 patients (average age 4.0 years old) with a total of 216 BTR visits (average visit time 64.75 minutes) were included. Scald burns were the most common mechanism of injury (76%), followed by flame (14%) and contact burns (7%). Most burns were superficial dermal (54%) and initially estimated at 5–10% TBSA (57%). A total of 38% of patients received surgical intervention. The majority of patients required intravenous sedation during dressing changes (72%), with the most common medication used for intravenous sedation being propofol (83%). Nine patients were converted from oral to IV sedation, 2 had short apnea periods that recovered spontaneously and 2 had prolonged sedation. Overall, there were no major sedation related complications. Interviews with 6 staff members revealed an overall positive experience and few safety concerns.

Conclusions Our findings are consistent with current reports from other burn facilities. The BTR at BCCH is a safe and effective way to treat burn patients, preventing what would historically require inpatient management.

304 TELEDERMATOLOGY: A STUDY COMPARING DIAGNOSIS AND MANAGEMENT OF DERMATOLOGICAL CONDITIONS IN THE EMERGENCY DEPARTMENT

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10.1136/jim-2016-000365.304

Purpose of Study Teledermatology is a growing practice that can potentially revolutionize the delivery of dermatology services. However, before its routine application, more research is needed to verify the outcomes and limitations of this health care service. The purpose of this study was to examine the use of teledermatology and to investigate its validity as a tool to aid physicians in emergency room consultations.

Methods Used Subjects with dermatological skin conditions were recruited from UC Davis Emergency Department. For each case of a skin condition, still images of the dermatological condition were taken through a HIPPA compliant platform. An emergency medicine physician assessed the subject directly and one board-certified dermatologist assessed the skin condition through examination of the still images and was blinded to the diagnosis rendered by the non-dermatologist physician until a diagnosis was finalized. The concordance of the diagnosis and treatment plan was compared.

Summary of Results There were a total of 55 subjects enrolled, 5 were excluded, 50 were analyzed. There were 29 males and 21females. 33 subjects were pediatric subjects. 30 subjects were non-Hispanic, 19 Hispanic, and 1 declined to answer. Of the 50 subjects, there was a change in diagnosis in 23 subjects, and a change in management in 33 subjects. Of note, 8 subjects had formal dermatology

consults, which highly corrleated with the diagnosis and mangement of the blinded dermatologist.

Conclusions From our teledermatology study looking at patients from the emergency department at UC Davis Medical Center we found that it is a reliable and accurate mode of providing dermatological care. A measure that we originally did not set out to measure, but came out as a consequence of our study was the correlation between a live dermatology consult in the emergency department for some of the subjects in our study and the still images viewed by a dermatologist. We found that the diagnosis and management was in agreement between the two dermatologists in the 8 patients that received formal consults by the emergency medicine physicians. Many studies in the past have shown that teledermatology is fast, convenient and reliable; our study now shows it is also very accurate.

305 ASSESSING CALIFORNIA INSURANCE NETWORK ADEQUACY IN GENERAL PSYCHIATRY

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10.1136/jim-2016-000365.305

Purpose of Study Health care reform has changed how patients, providers, and insurances interact in the hopes of improving health care access. A recent study in Washington, DC by the American Psychiatric Association suggests that insurance networks are inadequate in mental health care. According to California state law, an adequate insurance network must provide patients an appointment offer within 15 days for specialist appointments. This study examined network adequacy for outpatient psychiatry in large health insurance networks in Sacramento, CA.

Methods Used Contact information of general psychiatrists (n=136) was randomly sampled from the directories of three large health insurance networks. Over the course of July 25 to August 1, 2016, calls were made to the sampled phone numbers to assess whether the listed numbers were correct and whether the physician practiced general psychiatry. If these were both accurate, volunteers determined the soonest available appointment for general psychiatry. If physicians could not be reached on the first call, volunteers called at least 3 times and left voicemails with a call-back number.

Summary of Results Analysis is ongoing at the time of this abstract submission. Of the providers listed on the insurance directories, 29% of on-exchange providers (n=86) and 24% of off-exchange providers (n=50) gave the date of their soonest available appointment. Only 27% of all obtained dates (n=37) were available within 15 days of the first phone call to the provider. 55.8% of the on-exchange providers and 44% of the on-exchange providers declined new patient appointments, with the most common reason being that the physician was not accepting new outpatients.

Conclusions The three large health insurance networks in Sacramento were inadequate for the needs of patients seeking outpatient psychiatry appointments. This is particularly concerning, since mental disorder is the top chronic disease resulting in Sacramento County's inpatient care, and suicide and homicide rank within the top five causes of premature death in Sacramento County. This study demonstrates a need for greater access to mental health care, and greater accountability from insurance networks.

306 THE ASSOCIATION BETWEEN INSURANCE STATUS AND THE TRANSFER OF PEDIATRIC PATIENTS WITH MENTAL HEALTH DISORDERS FROM EMERGENCY DEPARTMENTS

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10.1136/jim-2016-000365.306

Purpose of Study Pediatric patients presenting to the Emergency Department (ED) with mental health disorders have nearly doubled over the past decade. Previous research has suggested that non-clinical factors, such as insurance status, are associated with differences in the care provided to these patients. This study examined the association between a child's insurance status and an ED's decision to admit locally or transfer to another hospital among pediatric patients with a primary mental health diagnosis.

Methods Used The Healthcare Cost and Utilization Project 2012 Nationwide Emergency Department Sample was used to examine pediatric patients aged ≤17 years with a primary mental health diagnosis across 950 hospitals. Survey-weighted multivariable logistic regression models adjusting for confounders including gender and hospital setting were used to determine the association between insurance and the odds of transfer relative to admission. Secondary analyses examined this relationship across several diagnostic categories.

Summary of Results A total of 20,080 pediatric ED visits for mental health disorders were included in analyses. Overall, patients with Medicaid (OR: 1.42, 95% CI: 1.11, 1.82) and patients with no insurance or self-pay, (OR: 3.32, 95% CI: 2.33, 4.74) had higher odds of transfer relative to local admission compared to those with private insurance. Among specific diagnostic categories, patients with Medicaid and patients with no insurance/self-pay had higher odds of transfer for the following diagnoses: Adjustment Disorders (95% CI: 1.24, 3.01; 95% CI: 2.36, 12.18), Anxiety Disorders (95% CI: 1.13, 2.07; 95% CI: 2.22, 10.68), Bipolar Disorder (95% CI: 1.20, 2.48; 95% CI: 3.30, 8.27), and Depressive Disorder (95% CI: 1.07, 1.77; 95% CI: 1.33, 3.04).

Conclusions Pediatric patients with a primary diagnosis of a mental health disorder presenting to EDs who have Medicaid or are without insurance are more likely to be transferred to another hospital than to be admitted and treated locally than similar patients with private insurance.

307 INSURANCE STATUS IS ASSOCIATED WITH AMBULANCE USE IN THE PEDIATRIC POPULATION

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10.1136/jim-2016-000365.307

Purpose of Study Ambulance services are a significant economic burden on the healthcare system and it is important

that the use of these services be reserved for clinically appropriate emergencies. Patients with Medicaid Insurance have been previously shown to use ambulance services at a higher rate than patients with private insurance among adults. The purpose of this study was to examine the association between insurance status and the use of EMS services among children.

Methods Used We included patients aged <=18 years who arrived at an emergency department (ED) between 2009 and 2012 using data from the National Hospital Ambulatory Medical Care Survey (NHAMCS). The primary outcome variable was whether the patient arrived by ambulance or other means (private vehicle or public transportation). Patient's insurance status was categorized into Private, Medicaid, Self-Pay/Uninsured and Other. Demographic variables included age, gender, race, ethnicity, insurance status and geographical region. Clinical variables included triage, chief complaints, diagnoses-based severity scores, recalibrated RePEAT scores and comorbidity and/or chronic condition status of the patient. We evaluated the association between the ambulance use and the patient's insurance status using a multivariable logistic regression model adjusting for patient's age, race/ethnicity, geographical region, RePEAT score and comorbidity/chronic condition status.

Summary of Results An estimated 128,939,246 children arrived at an ED from 2009 to 2012; 8,184,826 (6.3%) arrived by ambulance and 114,709,789 (89.0%) arrived by other means. Children in the EMS cohort were by older (90.7 mo. vs. 119.2 mo., $p<0.001$) and sicker (RePEAT score 1.14 vs. 1.02, $p<0.001$). Compared to privately insured children, adjusted odds of ambulance use were lower for Medicaid children (OR 0.82, 95% CI: 0.69–0.99) and higher for uninsured children (OR 1.48, 95% CI: 1.15–1.90).

Conclusions Children who arrive at an ED by ambulance or other means differ in demographic and clinical characteristics. We found that children with Medicaid were less likely to arrive to the ED by ambulance compared to similarly sick children having private insurance.

308 PEDIATRIC INTENSIVE CARE UNIT OUTCOMES AMONG CHILDREN ADMITTED FROM EMERGENCY DEPARTMENTS

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10.1136/jim-2016-000365.308

Purpose of Study Past research suggests that children admitted to Pediatric Intensive Care Units (PICUs) from referring hospital Emergency Departments (EDs) arrive sicker and have poorer outcomes than children admitted to PICUs from EDs located within the same hospital. However, previous studies have focused on single diagnoses or were confined to single institutions. To provide a more comprehensive evaluation, this study examined PICU admissions from referring and children's hospital EDs on severity of illness and risk adjusted outcomes across a national dataset.

Methods Used The Virtual PICU Performance System database and the Pediatric Index of Mortality 2 (PIM2) were used to retrospectively examine data from 2011 to 2013 to compare PIM2 scores, observed mortality, PIM2-predicted risk of mortality and ratios of observed to expected mortality between pediatric patients, ≤18 years of age, admitted to PICUs from referring and children's hospital EDs. Hierarchical multivariable logistic regression was conducted to compare the odds of mortality between children admitted from children's and referring hospital EDs.

Summary of Results Of 80,045 children admitted from the ED to 109 PICUs, 35.6% were admitted from a referring hospital ED and 64.4% were admitted from a children's hospital ED. Children admitted from referring hospital EDs were older ($p<0.001$), less likely to be male ($p<0.001$) and more likely to be Caucasian ($p<0.001$). Children admitted from referring hospital EDs were also more likely to be mechanically ventilated within their first hour in the PICU ($p<0.001$) and had greater odds of being admitted with a high-risk diagnosis (OR 1.07, 95% CI 1.01–1.13). In addition, children from referring hospital EDs had greater median PIM2 scores ($p<0.001$), greater median PIM2 predicted risk of mortality ($p<0.001$), higher average observed mortality ($p<0.001$) and higher ratio of observed to expected mortality (1.04, 95% CI 1.00–1.09 vs. 0.97, 95% CI 0.92–1.01).

Conclusions Children transferred to PICUs from referring hospital EDs have higher severity of illness and poorer outcomes compared to children admitted from children's hospital EDs.

309 ANTICOAGULATION USE, FIELD TRIAGE, AND OUTCOMES OF OLDER ADULTS WITH HEAD INJURY TRANSPORTED BY EMERGENCY MEDICAL SERVICES

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10.1136/jim-2016-000365.309

Purpose of Study To describe the characteristics and outcomes of adults 55 years and older with head trauma transported by emergency medical services (EMS) with a focus on those that do not meet physiological, anatomical, or mechanism of injury (Step 1–3) field triage criteria but are taking anticoagulant or antiplatelet medications.

Methods Used This was a retrospective study at 5 EMS agencies and 11 hospitals in Central California. We included patients 55 years and older with head trauma who were transported to a hospital by an EMS agency during 1/1/2012 to 12/31/2012. EMS charts were linked to ED and hospital electronic records. The primary outcome measure was traumatic intracranial hemorrhage (tICH) on cranial computed tomography (CT) scan. The secondary outcome measure was a composite outcome of death or neurosurgery.

Summary of Results Of the 2,110 transports, there were 162 patients (8%) that met field triage criteria. Of those 162 patients, 113 patients (70%) were initially transported to a trauma center, 26 patients (16%) had tICH on CT imaging and 14 patients (9%) had a composite outcome of death, or neurosurgery. Three patients (12%) with tICH and 5 patients (36%) with a composite outcome were not initially transported to a trauma center.

1,948 patients did not meet Step 1–3 criteria. Of these,

566 patients (29%) had anticoagulant or antiplatelet use. Out of those 566 patients, 52 patients (9%) had tICH on CT imaging (4 (8%) required neurosurgery and 7 (13%) died during hospitalization) and 15 (3%) had a composite outcome measure. 300 of the 566 patients (53%) were initially transported to a trauma center. 23 patients (44%) with tICH and 6 patients (40%) with a composite outcome measure were not initially transported to a trauma center.

Conclusions In our study of older adults with head trauma, relatively few patients met Step 1–3 triage criteria. In those who did not have Step 1–3 criteria, nearly 30% had anticoagulant or antiplatelet use with only about half of these patients being triaged to a trauma center. A relatively high proportion of these patients had tICH but a much smaller proportion had a composite outcome of death, or neurosurgery.

310 AN ANALYSIS OF GENERATIONS AND INTERGENERATIONAL CONFLICTS IN THE EMERGENCY ROOM

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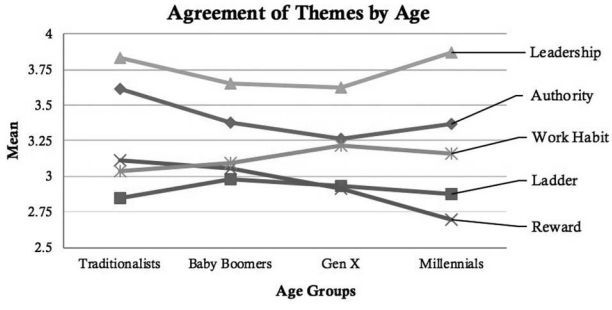
10.1136/jim-2016-000365.310

Purpose of Study The current work force is unique in that there are four generations working together simultaneously. This study aims to identify and elucidate the incidence of intergenerational conflicts between medical and health professionals in the emergency room setting. Conclusions made from this research will provide a foundation for a toolkit that establishes methods to mitigate conflicts and tensions in the ER.

Methods Used A survey was created and distributed to members of the American College of Emergency Physicians using Qualtrics®. The survey data was collected after 10 weeks and analyzed using STATA (n=805).

Summary of Results The study confirms that conflicts between generations of physicians and other health professionals occur in the emergency room, with 69.5% of respondents reporting conflict. The areas from which these conflicts arise are centered around themes of professionalism, collaboration, and training differences between the generations. Moreover, the survey exposes vital information about the characteristics or work values of the generations, demonstrating differences in generational perspectives from which conflicts have the potential to arise.



Abstract 310 Figure 1 Mean agreement to themes

Conclusions The presence of intergenerational conflicts contributes to the already existing stressful work environment of the emergency room. This research not only identifies key categories of conflict that occur between generations, but it also reveals five areas in which generations most significantly differ. By targeting these identified areas, methods and strategies can be developed to mitigate tensions that arise in the emergency room as a result of intergenerational conflicts. Moving forward, this research is fundamental in designing a toolkit that will outline these strategies, serving as a resource that improves the quality of care to patients and the satisfaction of emergency physicians.

311 REPRESENTATION OF WOMEN AMONG ACADEMIC GRAND ROUNDS SPEAKERS

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10.1136/jim-2016-000365.311

Purpose of Study Grand Rounds (GR), a time-honored method of disseminating clinical and research knowledge to medical audiences, showcases speakers as successful academic role models. Exposure to successful female role models, such as GR speakers, may positively impact retention of women in academic medicine. Thus, we sought to determine whether women's representation as GR speakers reflects their representation in academic medical workforces.

Methods Used We surveyed GR speaker series in clinical specialties containing >2% of US academic physicians, per Association of American Medical Colleges (AAMC) 2013–14 data. Specialties for which ≥15 institutions made Jan-Dec 2014 GR calendars available via websites/email were analyzed. For each GR session, we categorized speaker(s) by trainee status, institutional affiliation, and gender. Female speaker percentages were compared to AAMC workforce gender demographics using one-sample t-tests. Intramural and extramural percentages were compared via paired t-test.

Summary of Results Anesthesiology, Internal Medicine, Neurology, OB/GYN, Pathology, Pediatrics, Psychiatry, Radiology, and Surgery met inclusion criteria. Overall, GR presented by women ranged from 20.0% (Radiology) to 60.3% (OB/GYN) of sessions (median: 28.3%). Among sessions delivered by faculty or other non-trainees, female representation ranged from 19.6% to 53.3% (median: 26.2%). When compared to national academic medical workforces, these non-trainee female speaker percentages were uniformly statistically lower than the female composition of resident workforces, and lower than faculty workforces' female compositions in all specialties except OB/GYN and Surgery. Extramural speakers were less likely than intramural speakers to be women (median 22.4% vs. 29.0%; p=0.01). When female speaker percentages were normalized to workforce demographics' female percentages, median ratios were 0.56 for medical students, 0.61 for residents, and 0.79 for faculty.

Conclusions Women's representation among academic GR speakers falls below percentages of female medical

students, residents, and often faculty. As women's visibility in prestigious academic venues such as GR may subconsciously influence women's desires to pursue academic medicine, GR organizers may consider highlighting more female role models as GR speakers.

Hematology and Oncology II
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

312 RHOB LOSS DURING AGING CAUSES INCREASED C-MYC AND PROMOTES LUNG TUMORIGENESIS

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10.1136/jim-2016-000365.312

Purpose of Study Lung cancer is the leading cause of cancer-related death. Mutant K-Ras defines a distinct lung cancer subpopulation characterized by smoking. c-Myc is deregulated in virtually all cancers. RhoB is a tumor suppressor that inhibits cancer cell proliferation, invasion and metastasis, and its expression decreases with lung cancer progression. Inhibiting c-Myc has been shown to eradicate K-Ras driven lung cancer, while RhoB is decreased in lung tissue with age. Downregulation of c-Myc by RhoB via GSK3β pathway has been shown in murine cells, proposing that RhoB may serve as a therapeutic target to decrease c-Myc in lung cancers.
Methods Used A549, H157, MMEC or MEF cells were cultured and treated with vectors to induce: RhoB knockdown with shRNA, RhoB overexpression via pmKate2-RhoB fusion protein, or immortalization via Myc or E1A+Ras. Lung tissues from young and old C57/BL6 mice and tobacco specific carcinogen NNK-treated A/J mice were prepared for IHC and WB analysis.
Summary of Results In E1A+ Ras-transformed MEF cells, the RhoB nullizygotes did not express RhoB leading to an increase in levels of active Akt, inactive GSK3β, and c-Myc. In c-Myc immortalized MMEC cells, the RhoB heterozygotes had less RhoB expression than the homozygotes counterpart causing an increase in levels of active Akt, inactive GSK3β, and c-Myc. RhoB knockdown in A549 cells resulted in an increase in Akt activation, inactive GSK3β and c-Myc. RhoB knockdown A549 cells expressed less E-Cadherin and more Vimentin, suggesting that they progressed further along the Epithelial-Mesenchymal Transition. H157 cells with RhoB overexpression had decreased levels of active Akt, inactive GSK3β, and c-Myc. Results from in vivo experiments are pending.
Conclusions We were able to confirm that RhoB decreases c-Myc levels in murine cells and human cancer cells such that any downregulation of RhoB results in an increase of active Akt, inactive GSK3β, and c-Myc. Genetically restoring RhoB diminished c-Myc in a similar pattern to the cells that constitutively expressed RhoB further lending to the possiblity of utilizing RhoB as a therapeutic agent, especially in aged smokers.

313 KARYOMETRY IDENTIFIES A DISTINGUISHING FALLOPIAN TUBE EPITHELIUM PHENOTYPE IN SUBJECTS AT HIGH RISK FOR OVARIAN CANCER

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10.1136/jim-2016-000365.313

Purpose of Study Ovarian cancer is the deadliest reproductive malignancy in women with less than 30% of advanced disease patients surviving 5 years. High grade serous ovarian carcinoma is thought to originate from fallopian tube epithelium. Karyometry is a method of detecting chromatin abnormalities at the nuclear level using high-resolution computer imaging analyses. Previous karyometric studies have shown significant relationships between abnormalities in chromatin of intraepithelial neoplasms compared to their corresponding invasive cancers. This study hypothesizes that karyometry can detect nuclear abnormalities of fallopian tube epithelium in women carrying BRCA1 or BRCA2 gene mutations whose risk for ovarian cancer is high versus low.
Methods Used Fallopian tube tissue from 8 women at high risk for ovarian cancer due to BRCA1/2 and 7 women at normal risk were obtained from the tissue bank at NorthShore University Health System of the Evanston Hospital (University of Chicago). Tissues were fixed, paraffin embedded, sectioned and stained, followed by high-resolution imaging and karyometric analysis.
Summary of Results The distribution of nuclear features and nuclear signatures from women at high risk show a markedly greater deviation from normal. The two most segregating features in the discriminant function scores show a pronounced shift from normal for high risk nuclei and represent a statistically significant difference ($p<0.05$) between the two groups at the nuclear level.
Conclusions In conclusion, karyometry detected a morphometric phenotype in nuclei of fallopian tube epithelium of women at high risk for disease. Future blinded studies in larger numbers of high versus low risk women are required for validation of these potentially prognostic methods.

314 THE ROLE OF WNT LIGANDS IN THE PROGRESSION OF BRAF-DRIVEN LUNG TUMORS

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10.1136/jim-2016-000365.314

Purpose of Study Non-small-cell lung cancer is the leading cause of cancer mortality, resulting in over 150,000 deaths in the US per year. The $BRAF^{V600E}$ mutation leads to constitutive activation of the BRAF oncoprotein, and is expressed in 2–3% of these cancer types. Research has demonstrated that engagement of cell cycle arrest in benign

$BRAF^{V600E}$- induced adenomas is mediated by an insufficiency of WNT –> β-catenin –> c-MYC signaling. However, the source and nature of WNT ligands required for tumorigenesis remains unknown.

Our goal is to utilize RNAscope in situ hybridization (ISH) to identify which Wnt/β-catenin pathway genes dictate the development or maintenance of cancer cells, in addition to their source and time-course of expression.

Methods Used RNA probes for fourteen of the known WNT ligands, in addition to *Axin2* (downstream Wnt target), *Porcupine* (required for WNT secretion and activity), *CD45* (lymphocyte marker), and *CD68* (macrophage marker) were hybridized to lung tumors resected from 3, 6, and 12-week post induction $BRAF^{V600E}$ and $BRAF^{V600E}$ /$PIK3^{CAH1047R}$ mouse lines using RNAscope ISH.

Summary of Results WNT5a and WNT11, ligands both shown to be upregulated in resected NSCLC, were expressed in unique stromal-like patterns throughout tumors in 3, 6 and 12-week post induction lung sections. CD45, CD68, Porcupine, and Axin2 RNA was uniformly expressed in $BRAF^{V600E}$ expressing tumors. Furthermore, compared to $BRAF^{V600E}$ tumors, $BRAF^{V600E}$ /$PIK3C^{AH1047}$ co-expressing tumors had significantly upregulated RNA expression of these four genes.

Conclusions Wnt/β-catenin is an important signaling pathway in the microenvironment of lung tumor cells, however, the source of WNT ligands remains unknown. Using RNAscope ISH, we found that compared to $BRAF^{V600E}$ lung tumors, $BRAF^{V600E}$ /$PIK3C^{AH1047}$ co-expressing tumors expressed upregulated CD45, CD68, Porcupine and Axin2 RNA. This suggests the possibility that tumor cells are responding to a stromal source of WNT ligands, potentially arising from lymphocytes.

Understanding how Wnt/β-catenin plays a role in initiation of lung tumorigenesis and maintenance of tumor cell proliferation may contribute to novel therapeutic options for NSCLC patients.

315 CANCELLED

316 SMALL MOLECULES ENHANCE THE EFFECTS OF PROTON IRRADIATION ON GLIOBLASTOMA CELL LINE (U-138)

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10.1136/jim-2016-000365.316

Purpose of Study Glioblastomas, the most common type of brain tumor, are radioresistant, chemoresistant tumors which are almost always lethal. Current standard of patient care involves surgery, chemotherapy, and radiation targeting the tumor. Duocarmycin SA (DSA), a small molecule DNA alkylating agent, is a potent chemotherapeutic drug with extreme cytotoxicity that has not been widely used in cancer therapy. As a new approach to treating glioblastoma tumors we propose the administration of a nanomolar concentration of DSA combined with proton radiation to cause a combined cytotoxic effect that would maximize the dose to the target and minimize the dose to the surrounding tissues.

Methods Used In order to define exposure level-response relationships for protons and DSA, we treated glioblastoma (GBM) cells and normal human lung epithelial (HLE) cell with graded dose/concentrations of 250 MeV protons and DSA. Cell toxicity was evaluated by trypan blue exclusion assays and cell counting at 72 hrs. after treatment. To test the hypothesis of synergistic effects between DSA and protons we performed combined treatments using the same endpoints.

Summary of Results Results of our cytotoxic assay indicate that single 2 and 3 Gray (Gy) doses of proton radiation alone are insufficient to effect GBM and HLE cell death respectively. Exposure to radiation significantly increases the effectiveness of a 0.1 nM dose of DSA, decreasing the survival from 76% to 62% in GBM cells. This synergy continues at 0.5 and 1.0 nM DSA. At higher doses of proton irradiation, the cumulative effect continues on GBM cells in the presence of DSA. At a single 3 Gy dose of proton irradiation GBM cells have 62% survival. In combination with 0.1 nM DSA, the survival drops to 31%. HLE cells exposed to 3 Gy protons and 0.1 nM DSA survived at a greater fraction than GBM cells at 82%.

Conclusions In summary, these preliminary results support the hypothesis that DSA at sub-nanomolar concentrations can effectively enhance the radiosensitivity of GBM cells. The differential response of these two cell lines (GBM vs. HLE cells) to the action of DSA at low concentrations is promising from a toxicity standpoint.

317 RNF20 OVEREXPRESSION MAY CONFER CHEMOTHERAPY RESISTANCE IN ACUTE LYMPHOBLASTIC LEUKEMIA

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10.1136/jim-2016-000365.317

Purpose of Study Although there have been laudable advances in the treatment of pediatric acute lymphoblastic leukemia (ALL), with 5-year survival now over 80%, relapsed ALL remains a top cause of childhood mortality. Cancer is the second-highest cause of death in children 1 to 14, and leukemia causes the most cancer deaths. There is thus an urgent need to identify pediatric leukemia drug targets.

Mutations of epigenetic proteins are common in ALL, with more than 60% having an epigenetic-modifier mutation at relapse. This prompted us to subject five paired diagnosis and relapse ALL samples to histone profiling by mass spectrometry. One pair showed an unusual profile, with loss of H3K79 monomethylation and increased dimethylation at relapse. Histone dimethylation requires ubiquitination of H2B. Transcriptome analysis revealed increased expression of the H2B ubiquitin ligase RNF20 at relapse in the dimethylated sample, suggesting that this mechanism underlies the aberrant profile. This raises the possibility that increased RNF20 expression, H2B ubiquitination, and

H3K79 dimethylation cause drug resistance. RNF20 has previously been shown to be required in MLL-rearranged leukemias. This sample, however, lacked MLL rearrangement, pointing to a generalizable mechanism.

We hypothesize that overexpression of RNF20 confers chemotherapy resistance to ALL cells. If correct, this would allow a better understanding of the role of RNF20 in leukemia and support the development of RNF20 inhibitors beyond MLL-rearranged leukemias.

Methods Used Lentiviral vectors with RNF20-GFP and empty-GFP were transduced into five ALL cell lines: 2 with MLL-rearrangement and 3 without. Following transduction, cells were sorted for GFP. Upregulation of RNF20, H2b-ub, and H3K79me2 in experimental cells was verified by Western blot. Growth rate and response to chemotherapy were compared between the cell groups.

Summary of Results We have created the experimental and control viruses. We are now transducing the viruses into leukemia lines and expect to conduct the drug assay and growth monitoring in October

Conclusions RNF20 overexpression has been observed in relapsed ALL and can be experimentally achieved in ALL cell lines. Should our data demonstrate that RNF20 overexpression confers chemotherapy resistance in ALL cells, this would support the development of RNF20 inhibitors for ALL therapy.

318 THE CYTOTOXIC EFFECTS OF DUOCARMYCIN-SA ON GLIOBLASTOMA MULTIFORME CELL LINE

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10.1136/jim-2016-000365.318

Purpose of Study Glioblastoma Multiforme (GBM) are radioresistant and chemoresistant tumors which progress quickly with a poor prognosis. Current standard of care combines surgery, chemotherapy, and targeted radiation therapy. Duocarmycin SA (DSA), a DNA alkylating agent, is a potent and effective small molecule with extreme cytotoxicity that has yet to be tested in cancer therapy. DSA could be an attractive agent for treatment if its toxicity is characterized in normal and GBM cells.

Methods Used In order to define the exposure level response relationships for DSA, GBM and normal human lung epithelial (HLE) cells were treated with graded nanomolar concentrations of DSA from 0.1 nM to 100 nM of DSA for 72 hours to determine its cytotoxicity. The Trypan Blue exclusion assay and cell counting method was used to assess the cytotoxicity of graded nanomolar concentrations of DSA and characterize concentration response relationships. We also assessed the proportion of apoptotic and necrotic cells using flow cytometry for Annexin V and 7-AAD binding.

Summary of Results DSA induce a dose dependant reduction of cell survival on GBM cells concentrations as low as 0.1 nM resulted in a reduction in GBM cell survival of 25% with maximum effect at 1 nM DSA with 80% reduction in cell survival. For HLE cells, a 0.5 nM dose of DSA reduced cell survival by 45%. Concentrations in excess of 1 nM DSA results in no further reduction in cell survival for both cell lines reaching a plateau in the dose response curve.

DSA (0.5 nM) treatment of HLE cells was able to induce apoptosis (Annexin V positive cells) reaching a peak of 72% at 48 hrs post treatment there was also an exponential increase in necrosis (7-AAD positive cells) reaching 20.3% of at 72 hrs.

Conclusions Preliminary data indicates that GBM cells exhibit extreme sensitivity to DSA at very low (nanomolar) concentrations in a consistent concentration-dependent manner. HLE cell lines also exhibit some sensitivity to DSA. Ongoing work on the cell lines using flow cytometry will allow a more precise determination of the comparative cytotoxic effects of DSA on HLE and GBM cells.

319 EVALUATING THE QUALITY OF ONLINE RESOURCES FOR ESOPHAGEAL CANCER PATIENTS

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10.1136/jim-2016-000365.319

Purpose of Study Internet use is ubiquitous in today's society. For cancer patients, the internet can prove to be a powerful information resource. However, a lack of quality control for web-based resources presents a problem for both physicians and patients. This study aims to comprehensively evaluate the quality of online esophageal cancer patient resources.

Methods Used A previously validated website evaluation tool was used to analyze the quality of online cancer resources for patients. The term "esophagus cancer" was used to retrieve hits from the search engine Google and the meta-search engines Dogpile and Yippy. A "top 100" website list was compiled using pre-specified inclusion and exclusion criteria. Websites were evaluated for administration, accountability, authorship, organization, readability, content and accuracy. Inter-rater reliability was confirmed via kappa statistics. Results were analyzed via descriptive statistics.

Summary of Results The search term "esophagus cancer" returned over 500 websites. Of the top 100 sites, 93% disclosed ownership, sponsorship, and advertising. Only 35% identified an author and even fewer (31%) gave author credentials. Less than half (48%) cited resources but information was oudated, with 35% using more than 3 reliable resources. The average reading level was grade 12, with average readability ease at 37.

Over half of the sites provided a definition (54%), etiology (52%), symptoms (63%), detection (70%), and treatment (64%). Few provided accurate incidence/prevalence (28%), stage-specific prognosis (27%) or preventative information (17%). The term "esophagus cancer" produced a top 100 list that differed significantly in content from the "esophageal cancer" list, despite common interchanging of these terms.

Conclusions The aggressive nature and difficulty catching early stage disease makes it essential to provide esophageal cancer patients with appropriate and accurate resources to aid in decision-making. While many sites disclose ownership and provide accurate diagnostic, symptom, and treatment information, significant deficits exist. Of concern, many esophageal cancer sites are outdated, complexly written, lack authorship and accurate prognostic and prevention information. This study may help to inform patient-physician encounters and provide patients with tools to evaluate the quality of web-based resources.

320 CANCEROUS WEBSITES? ANALYZING THE QUALITY OF PROSTATE CANCER WEB RESOURCES

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10.1136/jim-2016-000365.320

Purpose of Study With the increasing availability of health information on the internet, more prostate cancer patients are using web-resources to inform themselves about their cancer. However, there is little regulation over website quality. Hence patients may receive out-of-date or inaccurate information which may negatively affect their decisions. It is essential for oncologists to understand gaps in resources so they can provide patients with information to make fully-informed decisions.

Previous studies analyzing internet resources for other cancer types have been performed using our standardized rating tool however it has not been used to analyze prostate cancer. The current study looks to systematically analyze the quality of websites accessed by patients with prostate cancer.

Methods Used The term "Prostate Cancer" was searched in Google and the metasearch engines Yippy and Dogpile, and the top 100 hits related to patient information were compiled from over 32 million hits. A standardized tool was used to examine 100 sites with respect to attribution, currency, usability, and content.

Summary of Results Of the top 100 websites relating to prostate cancer information, only 27 identified an author, of which 16 had their credentials displayed. The vast majority of websites disclosed ownership (97%). Over half of the websites did not include the date of the last update, and of those that did only 66% were current within 2 years. According to the Flesch Kincaid Grade level tool for readability, the majority (76%) of sites were found to be at a high school level, while 19% were at university level. Finally, content varied among websites. 9 out of 10 sites provided information on detection and work up as well as treatments, but only 14% of sites included information on prognosis. About 86% of the sites were able to present the information on prostate cancer objectively.

Conclusions The reliability of websites presenting prostate cancer information is questionable. There were noted deficiencies in attribution, currency, and readability. While information on detection and treatment is well-covered, information related to prognosis is lacking.

Infectious Diseases II
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

321 PRECLINICAL DEVELOPMENT OF NOVEL ANTIBIOTICS AGAINST GRAM POSITIVE BACTERIA

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10.1136/jim-2016-000365.321

Purpose of Study Antibiotics with new mechanisms of action are needed to treat drug resistant bacteria. This research focuses on novel compounds that inhibit the essential enzyme methionyl-tRNA synthetase (MetRS) found in Gram positive bacteria. The research involves lead optimization work to identify compounds with improved oral bioavailability, high potency shown by low Minimum Inhibitory Concentrations (MICs), and a good safety margin.

Methods Used MetRS inhibitors were synthesized by Dr. Fan's lab aided by structure-based drug design. Strains of bacteria were obtained from ATCC and tested for MICs following CLSI procedures. Additional assays used include measuring the Minimum Bactericidal Concentration (MBC), MIC shift in serum supplemented media, resistance frequency determination, and pharmacokinetic studies. Efficacy experiments: CD1 mice were infected IP with *S. aureus* (ATCC 29213). Mice received oral doses of compounds (75 mg/kg) at 1 hr and 12 hr post-infection. At 24 h, spleens were harvested to quantify colony forming units of *S. aureus*.

Abstract 321 Table 1 In Vitro Data

Compound	History	S. aureus (MSSA) MIC (μg/mL)	S. aureus (MRSA) MIC (μg/mL)	E. faecalis MIC (μg/mL)	Mammalian cells cytotoxicity CC50 (μg/mL)
1312	Original hit	1.91	6.0	0.21	>7.5
1614	Improved oral availability	1.25	2.5	0.94	14.8
1717	Improved potency	0.16	0.075	0.05	5.8
2093	Improved potency	0.021	ND	ND	>21.6
2144	Optimized lead	0.017	ND	ND	>11.3
Linezolid	Comparator drug	2.5	1.15	1.93	>33

Summary of Results In the past year, 75+ novel MetRS inhibitors have been synthesized. The table below shows initial hits compared to recent optimized leads. Compounds were compared in the murine systemic infection model. The logarithmic changes in CFUs from the spleens for the treated mice compared to vehicle control were as follows: **1717** (−0.38), **2093** (−0.85), **2144** (−1.11), and linezolid (−1.15). The changes for **2093, 2144**, and linezolid were statistically significant. MetRS inhibitors show low cytotoxicity in vitro and are well tolerated in mice when dosed for 10 days.
Conclusions Optimized MetRS inhibitors have MICs against *S. aureus* and *E. faecalis* that are lower than the antibiotic, linezolid. In a mouse model of systemic *S. aureus* infection, **2144**, was equally effective as linezolid. **2144** is a candidate for a first-in-class antibiotic for Gram positive infections.

322 DEVELOPMENT OF RECOMBINANT VARICELLA ZOSTER VIRUS CONTAINING REGULATABLE CRISPR-CAS9

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10.1136/jim-2016-000365.322

Purpose of Study Primary Varicella Zoster Virus (VZV) causes varicella (chickenpox) and becomes latent in the trigeminal and dorsal root ganglia. VZV can reactivate decades later to produce zoster (shingles) in the elderly. The VZV vaccine uses a live attenuated virus that also becomes latent and can reactivate later on in life to cause shingles and associated serious neurological complications. VZV affects more than one million people in the U.S. annually. The goal of this project is to control the expression of genes necessary for host reinfection by using the CRISPR-Cas9 system. We will use the Cas-9 protein and guide RNA (gRNA) sequence to edit the VZV genome, specifically, VZV open reading frame (ORF) 63 which is present as duplicate copy in ORF70. Expression of ORF63/70 is necessary for virus replication, and without them the virus cannot reactivate to produce shingles. By using the CRISPR-Cas9 system to edit the latent VZV genome in the host, we can control the expression of genes essential for virus reinfection. This study will be used as the basis for future studies aimed at preventing shingles.
Methods Used 1. Prepare a CRISPR-Cas9 expression vector in which sequence encoding Cas9 is fused to a destabilization domain (rendering the stability of the protein dependent on the common antibiotic trimethoprim) and recombine the modified CRISPR-Cas9 sequences into the VZV genome. The guide RNA will be driven by the human U6 promoter and Cas9 expression will be driven by VZV IE63/70 promoter.

2. Test the efficiency of editing VZV genomes in VZV-infected cells using mutant VZV expressing VZV-specific gRNA.
Summary of Results The destabilization domain has been cloned into the N-terminus and C-terminus of Cas9. These clones were characterized using DNA sequencing and Cas9 was found to be in reading frame. Cas9 destabilization domain clones have been successfully transfected into kidney epithelial cells (Vero cells) and the presence of Cas9 was detected by Western Blot.
Conclusions After recombining modified CRISPR-Cas9 and gRNA for ORF63/70 into the VZV genome we hope to see that genes necessary for host reinfection can be controlled by the CRISPR-Cas9 system in a regulatable manner.

323 EVALUATION OF *CLOSTRIDIUM DIFFICILE* INFECTIONS (CDI), BLOODSTREAM INFECTIONS (BSI), AND THE MICROBIOME IN PEDIATRIC ONCOLOGY PATIENTS

Nycz B, Dominguez SR, Ir D, Robertson C, Frank D. *University of Colorado School of Medicine, Boulder, CO.*

10.1136/jim-2016-000365.323

Purpose of Study Development of bloodstream infections (BSI) and *Clostridium difficile* infections (CDI) in pediatric populations with underlying malignancies are frequent complications associated with significant morbidity and mortality. The relationship between the development of these infections and changes in the gastrointestinal microbiome have not been well studied. The purpose of this study was to explore possible associations between microbiome composition and the development of such infections in a small convenience cohort of pediatric oncology patients at Children's Hospital Colorado.
Methods Used As part of an outbreak investigation, stool samples were collected on all patients admitted to the pediatric oncology floor from Oct – Dec 2012. Stool samples were tested for the *C. difficile* toxin B gene by PCR (Xpert© *C. difficile*, Cepheid, Sunnyvale CA). Bacterial profiles from patient stools were determined by broad-range PCR of 16S rRNA genes and phylogenetic sequence analysis. Differences in microbiome composition were assessed by a non-parametric multivariate analysis of variance (PERMANOVA) test using the Bray-Curtis index to assess microbiome dissimilarity. Differences in relative abundance of specific taxa were tested using a Wilcoxon rank based test.
Summary of Results At admission, 21% (n=9) of 42 patients were colonized with *C. difficile*, all of whom had a cancer diagnosis preceding their current health-care encounter. Additionally, 24% (n=10) of patients previously had or developed a bloodstream infection. Differences in overall microbiome composition were significantly associated with cancer type ($p<0.008$), admission type ($p<0.05$), bloodstream infection ($p<0.001$), and subsequent *C. difficile* infection ($p<0.04$). Significant differences in subjects with subsequent *C. difficile* infections, compared with those who did not develop *C. difficile* infection were observed in several bacterial families, including Bacillales ($p<0.002$), Clostridiaceae ($p<0.04$), and Fusobacteriales ($p<0.05$).
Conclusions Within this pediatric population, our results suggest that changes in microbiome composition are associated with, and may be predictive of, subsequent bloodstream and *C. difficile* infections. A prospective study is required to further explore these relationships.

324 EVALUATION OF ALTERNATIVE ZOSYN (PIPERACILLIN/TAZOBACTAM) INFUSION STRATEGIES

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10.1136/jim-2016-000365.324

Purpose of Study Piperacillin-tazobactam (PTZ) or Zosyn is a broad spectrum antibiotic that is widely used to treat a variety of infections. Several pharmacokinetic and pharmacodynamic studies have shown extended infusion (EI) over 4 hours to have improved patient outcomes compared to standard infusion (SI). Purpose of this is study is to evaluate safety and efficacy of alternative PTZ infusion strategies between EI over 4 hours and the SI over 30 minutes at Kern Medical.

Methods Used We performed a retrospective chart review of patients who received at least 48 consecutive hours of treatment with PTZ from 01/01/ 2013 to 02/01/2015 in the ICU. Two groups were identified: patients who received a SI of PTZ (30 minute infusion of 4.5 gram IV every 6 hours), and those who received an EI of PTZ (4 hours Infusion of 3.375 gram IV every 8 hours). The primary outcomes were hospital length of stay and 14-day mortality; secondary outcome was total drug acquisition cost of PTZ treatment. Data were analyzed using chi-square, Fisher's exact, and Wilcoxon rank sum with Stata® v.12.0. This study was IRB approved.

Summary of Results Demographics were similar between each group (gender, age, APACHE II score, renal function, and comorbid conditions) as well as indications for PTZ use. The median duration of hospital stay were not significantly shorter in patients who received EI comparing to SI (22 days vs. 23 days, respectively; $P=0.31$). Patients who received EI dosing had statistical significantly lower mortality at 14-day ($P=0.015$) and 30-day ($P=0.006$), despite having received less doses than patients in the SI group (14 doses vs. 22 doses, respectively; $P=0.0028$).

Conclusions It appears that extended infusion of Piperacillin-tazobactam is a suitable alternative to standard infusion as seen with a significantly lower mortality at 14-day and 30-day despite having received fewer doses of treatment.

325 ATTITUDES TOWARDS NOVEL HIV PREVENTION STRATEGIES AMONG FEMALE SEX WORKERS IN PUNE, INDIA

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10.1136/jim-2016-000365.325

Purpose of Study HIV prevalence among female sex workers (FSWs) in India is a significant public health concern, with an estimated HIV prevalence of up to 38% in some regions compared to the general adult population prevalence of 0.3%. PrEP and self-testing represent effective new HIV prevention strategies that have not yet gained widespread use in India.

Methods Used We conducted 2 focus groups of 8 and 12 FSWs, respectively, to evaluate acceptability of PrEP and HIV self-testing in Pune, India, a city with one of the largest red light districts in India. Translated transcripts were surveyed for preliminary themes and are being coded for qualitative elements using Atlas.Ti software.

Summary of Results A preliminary thematic analysis of the focus group sessions revealed that a number of the FSWs believed that PrEP would provide an advantage over condom-only prophylaxis by conferring increased control over their own protection. At the same time, a number of the women expressed concerns over medication accessibility, noting particularly the lack of private storage space, and the potential for drug side effects. The majority of FSWs also articulated preferences for a monthly injection over the daily pill, the only currently available method of PrEP administration. The FSWs further indicated discomfort with hypothetical vaginal rings and pessaries for PrEP delivery. The majority of FSWs expressed interest in blood-based self-testing methods when provided with peer support systems and continued access to physician-mediated clinic-based testing and care. Most FSWs indicated reluctance towards using a saliva-based self-testing method due to concerns that this would be misinterpreted to indicate potential oral transmission of HIV.

Conclusions Our preliminary results indicate that while PrEP and self-testing may be acceptable methods of HIV prevention among FSWs in India, barriers to uptake exist including concerns about access and confidentiality. Additional studies are needed to develop a more complete picture of the barriers and facilitators to PrEP and self-testing among the extended FSW community, including determination of the attitudes towards HIV prevention of the brothel keepers and long-term partners of the FSWs.

326 MENTAL HEALTH AND PSYCHOSOCIAL FACTORS AFFECTING ADHERENCE TO HIV TREATMENT IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW

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10.1136/jim-2016-000365.326

Purpose of Study Nearly 25 million people are living with HIV in sub-Saharan Africa, but only 29% know their HIV-positive status, receive antiretroviral therapy (ART), and are virally suppressed. An incomplete understanding of global mental health issues has been a major barrier to providing comprehensive HIV testing, care and treatment. Since mental health issues may be associated with decreased adherence to ART, we sought to conduct a systematic review of clinical studies that have measured the impact of mental health on ART adherence in sub-Saharan Africa.

Methods Used We performed a systematic review and meta-analysis of studies assessing mental health among HIV-infected adults receiving ART in sub-Saharan Africa. We searched PubMed and PsychINFO for relevant studies published before June 2016 with the terms: "mental health" or "depression" and "HIV" and "ART" and "sub-Saharan Africa". We included studies that reported numeric depressive symptom scores from a questionnaire or a clinical diagnosis of depression. We extracted data on

screening methods for depression and ART adherence from each study, as well as baseline depression rates and treatment outcomes.

Summary of Results We identified 12 studies that assessed depression and ART adherence among HIV-infected adults in sub-Saharan Africa. Among those studies, there was considerable heterogeneity with 8 methods used to measure depression, and eleven methods used to measure ART adherence. Adherence measures included pill counts, visit attendance and questionnaires. Studies were conducted in eight different countries at fifteen unique sites.

Ten of twelve (83.3%) studies reported that HIV-infected adults who were depressed or had depressive symptoms were 1.6–2.7 times more likely to have poor adherence to ART. The two remaining studies (16.7%) found no significant association between depression and adherence.

Conclusions Although studies were quite different, depression was associated with poor adherence to ART among HIV-infected adults in sub-Saharan Africa. A validated tool for assessing adherence in resource limited settings would better identify patients who could benefit from adherence-related interventions. All HIV-infected adults should be screened for mental health issues, which may help improve ART adherence and clinical outcomes.

327 DISSEMINATED GONOCOCCAL INFECTION MASQUERADING AS SYSTEMIC LUPUS ERYTHEMATOUS FLARE

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10.1136/jim-2016-000365.327

Case Report A 16 year female who had been recently diagnosed with systemic lupus erythematous (SLE) presents to the emergency department with one month history of right shoulder swelling and decreased range of motion in addition to left hand swelling and left index finger contracture. She had gradually increasing pain with minimal response to over the counter analgesics. On review of systems, she had no fever, weight loss, or trauma. She admitted to sexual activity, but insisted on consistent use of barrier contraceptives. In the emergency department, ultrasound was suggestive of bursitis and patient was admitted for pain control. MRI was performed which was suggestive of abscess versus complex bursitis. Rheumatology was consulted and recommended that aspiration of the right shoulder be done in order to rule out infection before starting pulse steroids for presumed SLE flare. Aspiration of the right subacromial joint revealed purulent drainage which required subsequent washout. Initial gram stain of the aspirate demonstrated rare gram negative coccobacilli.

Treatment was initiated with vancomycin and ceftriaxone pending culture results. All immunosuppressants were discontinued except low dose prednisone. Culture of the abscess eventually returned positive for Neisseria gonorrhoeae. Nucleic acid amplification testing of the urine also returned positive for N. gonorrhoeae. Vancomycin was discontinued and patient was given standard one time dose of azithromycin for coverage of Chlamydiae. After seven days of intravenous ceftriaxone, patient demonstrated near resolution of right shoulder and left hand swelling in addition to improved range of motion of right shoulder, left hand, and left index finger. Patient was discharged home to complete 2–3 week course of IV ceftriaxone for treatment of septic joint.

This case highlights the importance of considering disseminated gonococcal infection in young patients presenting with arthritis, even those with chronic arthritis. Although only occurring in 0.5–3% of those infected with N. gonorrhoeae, recognition is essential for adequate treatment. Moreover, as exemplified in this case, distinguishing between septic joint versus exacerbation of a chronic autoimmune disease is critical for the proper management of both conditions.

328 IMPLEMENTATION CHALLENGES OF POINT-OF-CARE TESTING: EVIDENCE FROM THREE CASE STUDIES IN AN INFECTIOUS DISEASE CENTER IN DURBAN, SOUTH AFRICA

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10.1136/jim-2016-000365.328

Purpose of Study Diagnostic point-of-care (POC) tests have become increasingly utilized in resource-limited settings because they provide timely information for clinical management and reduce the need for follow-up visits. Our objective was to describe the implementation challenges of changes in patient flow and health worker roles for sexually transmitted infections (STIs), tuberculosis (TB), and HIV POC services in a public clinic in Durban, South Africa.

Methods Used We conducted interviews with 20 clinic staff to ascertain the extent to which POC tests are implemented. We used time-in-motion methods to directly observe patients and practitioners over an eight-week period and descriptive statistics to compile and summarize the data.

Summary of Results In this study, POC testing was utilized for HIV screening and TB testing, but was not used for HIV viral load or STI diagnosis. For STI management, patients waited in five queues to complete a visit and had a mean total visit time of 1 hour 50 minutes. The average clinical appointment lasted 7 minutes. Among HIV patients renewing medications, patients waited a mean of 2 hours 35 minutes for 7 minutes with a nurse. A rapid TB test, which can be performed in 90 minutes, took an average of 4 hours 16 minutes. This caused enough delay that 40% of patients were asked to return the following day for the test results. Staff identified significant challenges to POC implementation for all three services including patient volume, long assay times, broken machine slots, and limited space.

Conclusions This busy urban clinic had several queues for STI management and chronic HIV care, which resulted in very long clinic visits. POC testing is not used in all services provided at the clinic, and in TB testing it often does not provide same-day results. STI and viral load POC tests are currently being assessed for future wide-scale implementation in low- and middle-income countries. However, existing clinic workflow, personnel, and capacity must be considered in order to deliver timely information for clinical management and improve patient care.

329 A CASE OF SIADH INDUCED BY DISSEMINATED CNS COCCIDIOIDOMYCOSIS

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10.1136/jim-2016-000365.329

Case Report Coccidiomycosis causing SIADH

Coccidioidomycosis is a fungal pathogen that has a history of repeated infections primarily in Southwestern United States and Northern Mexico. Manifestations of coccidioidomycosis infections can range from pneumonia to organ and tissue dissemination. Central Nervous System (CNS) Coccidioidomycosis has been described multiple times in the past, but has never been associated with hyponatremia. We describe a case of a 19 year old female with coccidioidomycosis meningitis after four months of field work in central California.

This patient presented to the emergency department with the complaint of an ongoing headaches and subjective fevers for 8 days. Vitals on admission were normal. She reported associated nausea and vomiting since the onset of her headache. During examination the patient had nuchal rigidity and positive Brudzinki's and Kernig's signs. Lumbar puncture was performed for suspected chronic meningitis and evaluation of intracranial pressure. Results were elevated opening pressure of 55 cm of H2O, and cytology showed a glucose of 17 with and elevated WBC of 2700 with pleocytosis. Gram stains of CSF were repeatedly negative. However, serum coccidioidomycosis serology resulted as IgM weakly reactive suggesting acute disseminated coccidioidomycosis meningitis. Therapeutic serial Lumbar punctures were performed in an effort to reduce intracranial pressure until on day 4 when pressures returned to normal. Continued daily labs were ordered and patient showed persistent hyponatremia as low as 120. IV-Fluid replacement was initiated because it was thought that the patient may be hypovolemic due to her history of emesis prior to admission. However serum osmolality was found to be decreased at 252 and urine osmolality was 485 with urine sodium of 92. All of which were consistent with SIADH. Patient was treated with fluid restriction and fluconazole 1000 mg daily. After two weeks of this therapy, the patient showed significant clinical improvement and sodium normalized. No such cases of SIADH induced by CNS coccidioidomycosis have been described in the current literature.

Morphogenesis and Malformations Concurrent Session 10:15 AM – 12:30 PM Friday, January 27, 2017

330 HOMOZYGOUS VARIANT IN *CDC7:* A NEW MOLECULAR ETIOLOGY FOR MEIER GORLIN SYNDROME

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10.1136/jim-2016-000365.330

Case Report Meier Gorlin Syndrome (MGS) is a clinically and molecularly heterogeneous primordial dwarfism syndrome with pre- and postnatal growth deficiency, patellar hypo/aplasia, microtia and variable other features. Biallelic mutations in multiple components of the pre-replication complex, *ORC1, ORC4, ORC6, CDT1*, CDC6 and a functionally distict gene,*CDC45,* have been described in MGS. We report biallelic novel variants in a 2 year old female with a severe MGS phenotype born to consanguineous Pakistani parents. Born at term with mild IUGR, her subsequent growth parameters are all 6 to 8 standard deviations below the mean. She has global developmental delay. Physical findings include sparse scalp hair, absence of eyebrows and lashes with normal but delayed dentition. She has hypoplastic patellae, small, shell-like ears and conductive hearing loss. She has a prominent nasal tip, full lips, labial hypoplasia, edema of her feet and a high squeaky voice. Homozygosity consistent with 4th degree relatives was noted on SNP microarray. Atypical MGS features prompted whole exome sequencing which found a homozygous biparental missense variant, p.A254G, in the gene CDC7 (cell cycle division 7), a gene closely related to others associated with MGS. This variant has not been reported in ExAC or other databases and the site is conserved from yeast through humans. The kinases, Cdc7, and cyclin-dependent kinases are required to establish replication forks during the initiation of chromosome replication, a process common to the initiation of cell replication in all organisms (Labib K, 2010). CDC7 closely interacts with several ORC subunits. Inactivation of Cdc7 in yeast results in arrest of cell growth (Kim JM *et al* 2003). Conditional inactivation of cdc7 in undifferentiated mouse embryonic stem cells leads to growth arrest with rapid cessation of DNA synthesis and is required for ongoing DNA synthesis. The mouse knockout is an embryonic lethal and surviving mice show severe IUGR, small organs, and severe gonadal abnormalities (Kim JM *et al* 2002).

This appears to be the first human *CDC7* phenotype and adds to the number of cell cycle related gene mutations causing Meier Gorlin syndrome.

331 A NOVEL AUTOSOMAL DOMINANT MICROCEPHALY SYNDROME DUE TO VARIANTS IN *KMT2B*

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10.1136/jim-2016-000365.331

Purpose of Study We report on two probands with similar phenotypes, both with heterozygous variants in *KMT2B* identified through whole exome sequencing. *KMT2B* is a member of the SET/MLL protein family and these proteins are important in cancer and other human disease (e.g. *KMT2D* is a cause of Kabuki syndrome). KMT2B/MLL2 is expressed ubiquitously in all adult tissues. It is expressed in various areas of the brain and has been proven to be necessary in the formation of memory in mice. The purpose of this article is to document a novel gene causing microcephaly and developmental delay and define the associated phenotype.

Methods Used Phenotypic data were extracted from clinical charts. Whole exome sequencing was performed in both individuals.

Summary of Results A two-year-old female was evaluated for global developmental delay, failure to thrive, and microcephaly. A *de novo* heterozygous variant in *KMT2B* (c.5724_5751del28; p.P1909Lfs*16) was identified on whole exome sequencing. The second case is a 16-year-old male who was evaluated for microcephaly, slurred speech, chorea, tremors, history of failure to thrive, and short stature. This boy was reported to have normal cognition but a history of motor regression. A *de novo* heterozygous variant in *KMT2B* (c.6245_6266dupGCACGCCTCCT TCGGGGCCAGG; p.V2090Hfs*25) was detected on whole exome sequencing for this individual.

Conclusions The two individuals had microcephaly, failure to thrive and motor impairment. The phenotypes are relatively non-specific but have similarities. Given the disparity of ages, further follow up of the younger child will be important to clarify the phenotype. However, the overlapping phenotypes of these two unrelated individuals with heterozygous variants in *KMT2B* suggest pathogenicity. Future functional studies and identification of additional cases will help confirm causation, clarify the phenotype, and the degree of variable expressivity.

332 GENETIC RE-INTERPRETATION REVEALS NOVEL *ARF1* VARIANTS IN BRAIN MALFORMATION INDIVIDUALS

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10.1136/jim-2016-000365.332

Purpose of Study Disorders of morphogenesis are common, but even with exome sequencing, most cases remain unsolved. Many variants are found on patient sequencing, but how should these be medically prioritized for clinical diagnostics? Phenotypic features from detailed examination can be used to generate a genetic differential diagnosis, or a gene differential can be created informatically to add to the phenotypic information. Here we describe a novel exome re-analysis process whereby all patient VUS and phenotypic information are used to assess the etiology for disease. We focus on amino acid substitution variants in these unsolved patient cases, as these variants are very numerous.

Methods Used At the UCSF Personalized Genomics Clinic, we reviewed undiagnosed genetic conditions over the past 3 years and identified brain malformation conditions for potential re-analysis. Clinical dysmorphology and exome data were obtained for re-analysis. For undiagnosed brain conditions, novel missense-depleted region (MDR) analysis was performed, ranking all proband missense variants. Variant functional testing was performed by mutating candidate gene expression constructs prior to testing in culture.

Summary of Results By using MDR prioritization, we identified top-ranked genes regardless of whether genes have been annotated for human disease. *ARF1* was highly ranked, and three independent patients with brain malformation conditions were identified with novel *ARF1* missense variants. These were found to all be *de novo*, and variants clustered at the active site of ARF1, as opposed to population variants. Protein functional analysis by site-directed mutagenesis demonstrated decreased protein activation, supporting that the mechanism is loss of protein function. Brain malformation was accompanied by developmental delay and ear malformation.

Conclusions The novel association of *ARF1* variants in brain malformation individuals expands the RAS group of conditions and links ARF1 to filamin A and other cytoskeletal mechanisms that are important in brain malformation. MDRs can enhance exome re-analyses and may be widely applicable to multiple unsolved conditions.

333 PRENATAL INFECTION BY THE ZIKE VIRUS. DELINEATION OF THE PHENOTYPES

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10.1136/jim-2016-000365.333

Purpose of Study ZIKV prenatal infection has affected thousands of children during the last 18 months in Brazil and other countries. In collaboration with the Brazilian Task force for ZIKV we have examined more than 200 children with ZIKV embryopathy. Delineation of the phenotypic features is aimed at understanding the mechanisms leading to brain diruption, neurologic impairment and significant dysmorphic features.

Methods Used We designed and reviewed our assessment protocols both for Dysmophology and Neurologic examinations, based on the experience with 83 children with brain imaging consistent with ZIKV prenatal infection with positive CSF ZIKV specific CSF serologies in 30 children. We designed scales of neurologic impairment in order to undertsnd the natural history of the disorder and its range of severity.

Summary of Results Intrauterine growth deficits were present in 30% of infants. Microcephaly was present in 70% at birth, and occurred later in many additional cases. Significant features involving redundant skin of the scalp (cutis gyrata, skin folds, furrows), and skull deformities with overlapping of sutures and bony prominences indicated skull collapse in greater than 50% of children. In those, a typical phenotype of Fetal Brain Disruption Sequence could be identified. Several dysmorphic features such as a creases in palms and fingers and hair patterns pointed to the gestational periods of the brain disruption. Generalized arthrogryposis was present in 10% of cases, but camptodatylyes and club feet were present in many more. Hypertonia with spasticity, decreased alertness with irritability, and profound developmental delay, poor vision and hearing were present in many infants.

Conclusions ZIKV prenatal infection is often a recognizable phenotype. Most often, dysmoprhic features and neurologic impairment are severe and predict important neurologic sequelae.

334 MATERNAL DIABETES-RELATED CONGENITAL MALFORMATIONS IN A POPULATION-BASED STUDY IN UTAH

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10.1136/jim-2016-000365.334

Purpose of Study Observational epidemiologic studies that investigate congenital malformations report many associations with genetic or environmental factors; however, only 2 studies have directly explored the etiology in clinically well-defined population-based cohorts. To this end we developed a multidimensional classification system that considers etiology, morphology, and pathogenesis as domains and applied the model to the Utah population-based birth defect surveillance network (UBDN). We have reported that 0.8% of the cases had the cause due to well established teratogens, and notably maternal diabetes (MD) was the most common etiology for the teratogenic group. In this paper we present the cases with malformations due to MD and propose a model for inferring causation in maternal diabetes-related malformations.

Methods Used We applied this classification system to assess a cohort with major malformations among all pregnancy outcomes in the UBDN, 2005–09. We then looked specifically at the infant cases with a malformation where the mother had pregestational diabetes and applied specific criteria: We concluded that MD was the cause when the case had a malformation (or pattern) known to be strongly associated with maternal diabetes based on clinical and epidemiologic evidence (holoprosencephaly, caudal dysgenesis, microtia, heterotaxia, multiple vertebral defects, femoral hypoplasia) or with strong epidemiologic evidence (anorectal defect, bilateral renal dysgenesis). We excluded cases where the malformation was not characteristic (e.g., isolated cleft lip).

Summary of Results Among all cases in the UBDN with MD, we identified 34 cases that met our strict criteria for cause. 29 had multiple congenital anomalies (MCA), and 5 were isolated defects. Multiple vertebral defects (7) and caudal dysgenesis (8) represented the largest numbers of cases.

Conclusions We used a combination of clinical and epidemiologic evidence to decide whether to conclude causation where the mother had pregestational diabetes. We propose the use of these strict criteria in population studies of congenital malformations as an additional analytic strategy.

335 PRADER-WILLI SYNDROME WITH UNANTICIPATED RENAL COMPLICATIONS

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10.1136/jim-2016-000365.335

Purpose of Study Prader-Willi Syndrome (PWS) is a neurodevelopmental condition with specific healthcare surveillance recommendations. Several organ system anomalies have been observed, but renal involvement, in particular, in PWS has been sparsely mentioned. Here we examine the association of PWS and renal disease, and describe a second case of Focal Segmental Glomerulosclerosis (FSGS) in PWS with a single visualized kidney. We compare six other cases of PWS with renal disease and analyze the histopathology and accompanying renal involvement patterns. We also assess the 15 q critical region for potential candidate genes that could contribute to renal involvement.

Methods Used To evaluate instances of renal disease in PWS, we reviewed the literature using Pubmed. Two readers assessed literature review. We reviewed renal histopathology, laboratory parameters, genomic alteration, and demographics. Genomic testing for our new patient was done via SNP microarray: 4.9 Mb deletion of the PWS region.

Summary of Results In addition to our patient, we found six additional reports of PWS with renal disease. The renal findings ranged from membranoproliferative glomerulonephritis, FSGS, IgA nephropathy and end stage renal disease. We present an 11 year-old female without a prior diagnosis of PWS, who presented with edema and respiratory distress, BUN 153 and creatinine 17.3. She promptly required hemodialysis. The patient had developmental delay, obesity, high blood pressure, almond shaped eyes, tapered short fingers. She was anemic and had severe metabolic acidosis. Abdominal ultrasound showed one visualized hyperechoic kidney. Biopsy had histopathologic findings of FSGS.

Conclusions This is the second PWS patient described with FSGS, and interestingly both individuals had only one visualized kidney, one presented at age 16 and our patient at age 11. Out of seven patients with PWS renal disease, six were females. The presence of single kidney might magnify the risk, as four patients had single kidneys. Obesity and hypertension may also play a role. From this study, we suggest expanding health surveillance recommendations for PWS patients that may be susceptible to renal complications. Renal assessment and urine analysis for PWS patients could help detect early renal involvement, and earlier intervention could decrease the chance of developing ESRD, which would impact patients' quality of life.

Neonatology General IV
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

336 NEURODEVELOPMENTAL OUTCOMES AFTER ADMINISTRATION OF LATE SURFACTANT IN THE TOLSURF TRIAL

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10.1136/jim-2016-000365.336

Purpose of Study TOLSURF randomized 511 extremely low gestational age newborns (ELGAN) ventilated in the second week of life to late surfactant vs. placebo, representing a high risk group for later neurodevelopmental impairment (NDI). To assess safety of late surfactant, cognitive, motor, hearing, and vision status were assessed at 24

months corrected age.

Methods Used Children were evaluated in person or via telephone interview (if unable to return to study center). Motor impairment was defined as a Gross Motor Function Classification System score of ≥2, hearing impairment as bilateral hearing loss requiring amplification, visual impairment as bilateral blindness, and moderate-to-severe cognitive impairment as a Bayley-3 cognitive score <85. NDI was determined if cognitive, sensory, and motor outcomes were collected and one or more impairments was identified. As a secondary outcome, motor impairment was evaluated alone.

Summary of Results 322 infants (72% of expected) underwent Bayley-3 testing (median corrected age 24.4 months, range 18.7–60.3) and also had motor, vision, and hearing outcomes evaluated for determination of the composite outcome. There was no difference in rates of NDI by treatment with late surfactant (27.9% vs. 31.5% for late surfactant vs. control; OR 0.85; 0.51, 1.41). 415 infants (93% of expected) were evaluated for motor impairment, with no difference in rate by late surfactant treatment (8.7% vs. 8.2% for late surfactant vs. control; OR 1.06; 0.53, 2.1).

Conclusions Treatment with late surfactant had no detrimental effect on neurodevelopmental outcomes in a high risk population of ELGAN. The extensive respiratory severity data collected from this cohort further offers opportunities to investigate associations between respiratory outcomes and neurodevelopmental status in early childhood.

337 LIMB PROPRIOCEPTIVE STIMULATION STABILIZES CARDIORESPIRATORY PARAMETERS WITHOUT DISRUPTING SLEEP IN PREMATURE NEONATES

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10.1136/jim-2016-000365.337

Purpose of Study Apnea of Prematurity (AOP) and intermittent hypoxia (IH) are common, affecting the majority of premature infants. Repeated episodes of IH during apneic episodes exert significant changes to sympathetic nerve activity, leading to substantial changes in blood pressure (BP). We found that neuromodulation of limb proprioceptive afferents using a vibration device was associated with fewer apneas, IH, and bradycardic episodes. Therefore, we hypothesized that, with proprioceptive stimulation, apnea-related BP changes would be reduced and there will be fewer sleep state disruptions.

Methods Used Premature infants (<36 wks gestation), with evidence of AOP were enrolled. Small vibration devices were placed on one hand and one foot, and activated in a 12 hour ON/OFF sequence for 72 hours. Heart rate, respiratory rate, oxygen saturation (SpO_2), amplitude integrated electro-encephalogram (aEEG), and continuous BP, derived from pulse transit time, were collected. We also assessed effects on pain and sleep using the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) and aEEG. Physiological changes were assessed by ANOVA, and N-PASS values by Chi Square.

Summary of Results 1. Significantly fewer breathing pauses, SpO_2 declines and bradycardic events occurred during vibration periods, compared to no-vibration periods 2. Acute falls in mean BP after apneas were substantially reduced during vibration periods, vs. no-vibration periods (Figure 1). 3. Fewer arousals occurred during vibration periods

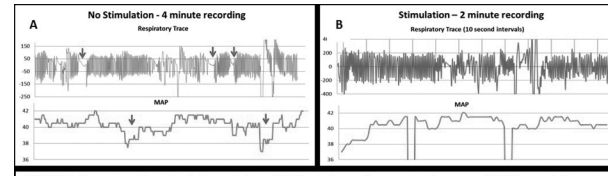

FIGURE 1: Proprioceptive stimulation maintains BP. Respiratory and mean arterial pressure (MAP) traces during a 4 min no-vibration (A) and 2 min vibration period (B) in a 28 wks GA infant. Respiratory pauses (red arrows) during (A) were accompanied by acute falls in MAP (red arrows) soon after breathing pauses. Stimulation, (B), diminished apnea periods, resulting in fewer BP declines.

Abstract 337 Figure 1

Conclusions Proprioceptive stimulation reduced apnea, bradycardia, and desaturation episodes, as well as accompanying BP changes while disruptions of sleep declined. This low-cost neuromodulatory procedure using vibration to proprioceptive nerves has the potential to provide a non-invasive intervention to stabilize BP in premature neonates with enhanced sleep integrity, thereby improving neurological outcomes.

338 SIX YEAR DEVELOPMENTAL ASSESSMENT OF FORMER PRETERM INFANTS TREATED WITH ERYTHROPOIESIS STIMULATING AGENTS

Milner CC,[1] Lowe J,[1] Cannon D,[1] Phillips J,[2] Caprihan A,[2] Wiedmeier S,[3] Patel S,[3] Steffen M,[1] Yeo R,[1] Campbell R,[1] Baker S,[3] Gonzales S,[2] Ohls RK[1]. [1]*University of New Mexico, Albuquerque, NM;* [2]*MRN, Albuquerque, NM;* [3]*U of Utah, Salt Lake City, UT.*

10.1136/jim-2016-000365.338

Purpose of Study We reported improved neurodevelopmental outcomes at 3.5–4 years among infants randomized in a multisite study to receive erythropoiesis stimulating agents (ESAs). This study aimed to determine if cognition continued to be higher at 6 years in former preterm ESA compared to placebo recipients.

Methods Used Former preterm infants randomized to ESAs or placebo were enrolled in the BRITE (Brain Imaging and Developmental Follow up of Infants Treated with Erythropoietin) study. Children born at term were enrolled as controls. Children were evaluated at 5.5–6 years using the Wechsler Preschool and Primary Scale of Intelligence (WIPPSI). Tests of EF and Visual-Motor skills were performed.

Summary of Results Of the 80 children born preterm and evaluated at 2 years, 57 enrolled in the BRITE study (43 ESA, 14 placebo). Twenty one term controls (TC) were enrolled. ANOVA revealed higher scores in ESA in full scale IQ (FSIQ [mean]: placebo: 81.64; ESA: 94.4, $p=0.021$) and performance IQ (PIQ: placebo: 82.64; ESA: 97.7, $p=0.002$). Univariate analyses indicated TC scored higher than placebo in FSIQ ($p<0.001$), PIQ ($p<0.001$), and verbal IQ ($p=0.021$), but not higher than ESA in these measures. EF tests revealed higher scores on cognitive flexibility for ESA compared to placebo ($p=0.013$). TC had higher scores on visual-motor integration (VMI) compared

to placebo (p=0.024). There was no statistical difference between ESA and term on VMI.

Conclusions Infants randomized to ESA continue to have significantly better cognitive outcomes and improved executive function at 5.5–6 years compared to placebo. Remarkably, scores in ESA recipients are similar to term children in measures of IQ. We speculate that ESAs may improve long-term executive functioning and cognitive outcomes of premature infants.

339 LACK OF A UNIFYING DIAGNOSIS: WHOLE EXOME SEQUENCING IDENTIFIES 2 *DE NOVO* MUTATIONS IN A PATIENT WITH A COMPLEX PHENOTYPE

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10.1136/jim-2016-000365.339

Case Report Proband is a 30-week premie who was noted in NICU to have a white forelock and abnormal stooling pattern. A diagnosis of Waardenburg-Shah syndrome was considered though no molecular testing was done.

By his first birthday, he was stooling regularly. At 19 months, he was seen by GI and diagnosed with GERD and "slow transit constipation". Though he passed his newborn hearing screen, he underwent visual reinforcement audiometry at 11 and 13 months of age, both of which were inconclusive. A sedated ABR was recommended, but deferred by parents. Ophthalmology evaluation at 22 months noted telecanthus with displaced punctate as well as delayed visual maturation, nystagmus and exotropia.

At 17 months of age, Bayley Scales of Infant and Toddler Development gave an age equivalent of 2.3 months to 6 months. Head MRI was recommended, but deferred at parents request. He had a mild lactic academia, with otherwise normal metabolic studies.

At 22 months of age, he was referred to Genetics for global developmental delay. He was not yet sitting independently and was non-verbal. Family history was significant for the father having a hypopigmented patch of hair with no history of hearing loss.

Weight, height and head circumference were appropriate for age. He had a broad forehead with no visible hypopigmented hair. Both the inner and outer canthal distances were >97th %ile. Interpupillary distance could not be measured. Eyebrows had a medial flare. He had a depressed nasal bridge and short, flat nasal tip with a tented upper lip and mild micrognathia. He had deep palmar and IP creases and overriding second toes. A faint hypopigmented patch was noted on the chest. He had generalized hypotonia, minimal expressive language and a raking grasp.

Microarray showed no clinically significant abnormalities. Whole exome sequencing (WES) revealed a pathogenic variant in the *PAX3* gene (R262X) and a likely pathogenic variant in the *PURA* gene (P260L). Both variants were *de novo*.

Mutations in *PAX3* are associated with Waardenburg syndrome type 1 while mutations in *PURA* are associated with hypotonia and neurodevelopmental delay. The results of the WES are consistent with our patient's phenotype and were able to give a diagnosis in spite of our search for a unifying diagnosis to explain our patient's features.

340 EARLY DIAGNOSIS AND TREATMENT OF PRADER WILLI SYNDROME: IS NEWBORN SCREEN FEASIBLE?

Singh P,[1,2] Nalbandian A,[1,2] Weiss L,[2] Oakes M,[3] Hossain W,[4] Butler M,[4] Kimonis V[2]. *[1]UC Irvine, Orange, CA; [2]UC Irvine, Irvine, CA; [3]UC Irvine, Irvine, CA; [4]Kansas University Medical Center, Kansas City, KS.*

10.1136/jim-2016-000365.340

Purpose of Study Prader-Willi syndrome (PWS), affecting 1/15,000 individuals, is a genetic disease characterized by lack of expression of genes on the paternal chromosome 15q11-q13 region. Clinical presentation range from hypotonia and feeding problems in neonatal period; short stature in childhood to hyperphagia, obesity and behavioral problems in adolescents. Growth hormone replacement has revolutionized the stature/body composition and behavioral outcomes in PWS individuals who have started treatment early. Despite significant diagnostic advances, the mean age for diagnosis of PWS continues to lag behind. California Newborn Screening (NBS) program tests for many metabolic and genetic disorders allowing for early diagnosis and management. Disorders are being added to the NBS program, PWS meets all the criteria except for the economical method of testing. We propose Methylation-specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) will be a time and cost effective test for PWS allowing for early diagnosis and treatment leading to lower morbidity and mortality and improved prognosis of PWS patients.

Methods Used DNA was isolated from newborn screening filter paper card using a modified combination of GenSolve and Qiagen DNA MicroKit. PWS testing was performed using MS-MLPA probe mix followed by fragment analysis using a 3730xl DNA analyzer.

Summary of Results We were able to extract sufficient amount of DNA from dried blood spot on newborn screening filter paper. PWS testing done on 10 patients and 6 controls. MS-MLPA was able to correctly identify 100% of PWS patients, able to differentiate between deletion and non-deletion in 100% and correctly identify the type of deletion in 80% of the patients.

Conclusions Initial data is promising that MS-MLPA testing can be used to diagnose PWS patients and identify the type of deletion from the DNA extracted from newborn screen filter paper. Next step would be to use new digital MLPA probe mix ME028-X3 from MRC Holland with Next generation Sequencing, which may prove to be more time and cost effective in testing PWS in newborns.

341 ELECTRICAL CARDIOMETRY IN PREDICTING RESPONSE TO IBUPROFEN TREATMENT FOR PATENT DUCTUS ARTERIOSUS AMONG VERY LOW BIRTH WEIGHT INFANTS: A PROSPECTIVE STUDY

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10.1136/jim-2016-000365.341

Purpose of Study Ibuprofen is commonly used for closure of hemodynamically significant patent ductus arteriosus

(hsPDA) in very low birthweight (VLBW, <1500 gm) infants. Electrical cardiometry (EC) is an impedance-based monitor that provides noninvasive cardiac output (CO) assessment. Previously, we demonstrated an acceptable agreement between EC and echocardiogram in VLBW infants with hsPDA. Since supranormal CO is a marker of the presence of a large PDA and large PDA in turn is predictive of decreased response to ibuprofen, we hypothesize that EC will predict ductal closure in response to ibuprofen in VLBW infants.

Methods Used We enrolled VLBW infants with hsPDA who were going to receive ibuprofen at Chang Gung Momorial Hospital (Taoyuan, Taiwan). HsPDA was defined as ductal diameter ≥1.5 mm±a left atrium to aortic root ratio (LA/Ao) ≥1.5. Either oral or intravenous ibuprofen was given at dosage of 10, 5, 5 mg/kg at a 24-hour interval. EC (Aesculon, Osypka Medical) was applied 1 hour prior initiating ibuprofen. Treatment response was defined as closure of PDA within 72 hours of completing the treatment.

Summary of Results Total 28 VLBW infants were enrolled. Their gestational age, birth weight, and age at the time of starting ibuprofen were 27.6±1.8 weeks, 973±219 gm and 4.7±3.1 days, respectively. PDA size and LA/Ao were 2.21 ±0.56 mm and 1.57±0.23, respectively. Eleven infants (39%) closed their ductus post treatment. Infants who closed their ductus were more mature (28.7±1.8 vs. 26.9 ±1.5 weeks, P=0.01) and had smaller weight-adjusted PDA (2.7±0.9 vs. 1.9±0.5 mm/kg, P=0.01) and lower CO (236±50 vs. 266±26 ml/kg/min, P=0.049). Using CO of 248 ml/kg/min as a cut-off value to predict the response, there was a sensitivity of 0.82 and specificity 0.73 (AUC 0.749, P=0.029).

Conclusions More mature VLBW infants, smaller PDA and lower CO are predictive of ductal closure with ibuprofen treatment. Monitoring CO by EC may be useful in predicting treatment response in VLBW infants with hsPDA.

342 SPLANCHNIC TISSUE OXYGENATION IS AFFECTED IN PREMATURE BABIES WITH PATENT DUCTUS ARTERIOSUS

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10.1136/jim-2016-000365.342

Purpose of Study Patent ductus arteriosus (PDA) is associated with a 2–5 fold increased risk for developing necrotizing enterocolitis (NEC). The proposed link between NEC and PDA is "diastolic steal" where blood flows in reverse from the splanchnic arteries back into the aorta causing intestinal hypo-perfusion. Near Infrared Spectroscopy (NIRS) can be utilized to non-invasively assess regional oxygen saturations (rSO_2) in the splanchnic and cerebral vascular beds of infants. The objective of this study is to determine whether infants with PDA born at <32 weeks gestational age (GA) and on full enteral feedings have impaired intestinal oxygenation compared to control infants.

Methods Used This study includes infants born <32 weeks GA, ≥14 days of life, on full volume enteral feedings with a moderate or large PDA diagnosed via echocardiogram at the time of monitoring. Control infants met the same inclusion criteria, without PDA. Cerebral (C) and splanchnic (S) rSO_2 were monitored using NIRS for 48 hours. Average values were calculated for the periods immediately preceding, during, and after each feeding. From these values, the splanchnic cerebral oxygenation ratio (SCOR) was calculated. Data was analyzed using ANOVA and Tukey's multiple comparisons test.

Summary of Results Twelve Infants were evaluated (6 in each study group). The PDA group had a median GA of 27 (25–28) weeks with a mean birth weight of 970±260 g. The Control group had a median GA of 28 (27–31) weeks and mean birth weight of 1321±368 g. The average baseline SCOR in babies with PDA was significantly lower than in control babies (0.64±0.2 vs. 0.76±0.1; $p<0.0001$). The average baseline S-rSO_2 was significantly lower in PDA babies vs. control babies (45.2±12 vs. 52.2±8; $p<0.001$). There was no significant difference in C-rSO_2 between the two groups (71.7±11 vs 68.3±6).

Conclusions Our preliminary results demonstrate a decreased SCOR and S-rSO_2 in premature infants with PDA in the time preceding enteral feedings. We speculate that this low baseline SCOR and S-rSO_2 will persist- or even worsen- during enteral feedings, a time of increased metabolic demand. This could contribute to the predisposition of neonates with PDA to develop NEC.

Nephrology and Hypertension Concurrent Session 10:15 AM – 12:30 PM Friday, January 27, 2017

343 INITIAL EXPERIENCE WITH THE BACTERIAL ENZYME IDES (IGG ENDOPEPTIDASE) FOR DESENSITIZATION OF HIGHLY HLA-SENSITIZED KIDNEY TRANSPLANT PATIENTS

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10.1136/jim-2016-000365.343

Purpose of Study Donor specific antibodies (DSAs) create an impenetrable immunologic barrier to transplantation. Current therapies aimed at modification of DSAs are limited and not effective in the most highly-HLA sensitized (HS) patients. The IgG degrading enzyme derived from *Streptococcus pyogenes* (IdeS) cleaves human IgG into F (ab'), and Fc fragments thus inhibiting complement dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). This suggests that IdeS could be useful for desensitization. Here we report our experience using IdeS for desensitization and incompatible transplantation.

Methods Used 15 HS patients received IdeS immediately before kidney transplantation). Frequent monitoring for

adverse events, alloantibodies, DSAs and renal function was performed. Post-transplant immunosuppression consisted of tacrolimus, mycophenolate mofetil and steroids. Patients received induction with Campath-1H. Patients also received IVIg+rituximab post-transplant to prevent antibody rebound.

Summary of Results All patients were highly-HLA sensitized (mean PRA 93%). Patients received IdeS infusion 4–6 hours prior to incompatible transplant. At transplant, total IgG and HLA antibodies were eliminated. Fourteen of 15 patients were successfully transplanted without discernable adverse events. Antibody-mediated rejection occurred in 4 patients at mean 3.6M post-transplant. All responded to treatment. One graft loss, mediated by non-HLA IgM and IgA antibodies, occurred.

Conclusions 1) IdeS treatment completely eliminates DSAs and allows for successful transplantation of HLA incompatible patients. 2) IdeS is well tolerated with acceptable adverse events. 3) IdeS may provide a more rapid and durable method to desensitize HLA sensitized patients, offering them the benefits of life-saving transplantation.

344 METHODS FOR IN VIVO DETECTION OF AUTOPHAGY IN POLYCYSTIC KIDNEY DISEASE (PKD)

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10.1136/jim-2016-000365.344

Purpose of Study Autophagy is a process that keeps cells alive under stressful conditions. In autophagy there is the sequestration of damaged organelles into double-membraned autophagosomes that subsequently fuse with lysosomes where their cargoes are delivered for degradation and recycling. Complementary methods that each assess different aspects of the process were used to detect autophagy

Methods Used 90 d old Pkd1 −/− mice (early PKD) and wild type mice (+/+) were studied. Proteins were measured by immunoblot analysis. 1) Autophagic flux: Microtubule-associated protein 1A/1B-light chain 3-I (LC3-I) is conjugated to form LC3-II, which is recruited to autophagosome membranes. To investigate whether there is increased autophagosome synthesis or decreased degradation by the lysosome, mice were treated with the lysosomal inhibitor, bafilomycin. 2) p62: p62-bound polyubiquitinated proteins are incorporated into the autophagosome and degraded in autolysosomes, serving as a readout of autophagic degradation. Increased p62 correlates with inhibition of autophagy. Increased p62-caspase-8 interaction mediates a shift from autophagy to apoptosis. 3) Transmission EM (TEM): Autophagosomes and autophagolysosomes (autophagosomes fusing with lysosomes) were visualized on TEM.

Abstract 344 Table 1 Immunoblot analysis intensity

Kidneys	+/+	+/+Baf	Pkd1 −/−	Pkd1 −/− Baf
LC3-II	++	+++	++	+
p62	+	+	+++	+++
CC-8	+	+	+++	+++
CC-3	+	+	+++	+++

Baf=Bafilomycin

Summary of Results See Table. 1) Autophagic flux: In +/+ kidneys, the amount of LC3-II was increased with bafilomycin suggesting increased autophagic flux. In Pkd1 −/− kidneys, the amount of LC3-II decreased with bafilomycin suggesting a decrease in autophagic flux. 2) p62: In Pkd1 −/− kidneys there was increased p62 that suggests inhibition of autophagy. In the same Pkd1 −/− kidneys, there was a large increase in cleaved caspase-8 (CC-8) and cleaved caspase-3 (CC-3), a marker of apoptosis. 3) TEM: In Cy/+ rats and cpk mice with PKD, autophagosomes, autophagolysosomes and mitphagy (autophagosomes containing mitochondria) were detected on TEM in renal tubular cells.

Conclusions Autophagy is decreased in PKD kidneys as evidenced by decreased autophagic flux, increased p62 and increased cleaved caspase-8

345 CLINICAL BIOMARKERS OF CHILDHOOD NEPHROTIC SYNDROME PREDICT UNFAVORABLE DISEASE

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10.1136/jim-2016-000365.345

Purpose of Study Nephrotic syndrome (NS) is a common childhood kidney disorder. Most cases are due to minimal change disease (MCD), while a minority has focal segmental glomerulosclerosis (FSGS) and an unfavorable clinical course, requiring a kidney biopsy to confirm. We hypothesized that clinical characteristics at diagnosis accurately predict FSGS.

Methods Used This was a case control study (1990–2012). Inclusion criteria included age 1–17 years, meeting the diagnostic criteria for NS, and having FSGS or MCD either presumed or diagnosed by kidney biopsy. Clinical characteristics at diagnosis included age, kidney function (eGFR), hypertension, hematuria, nephritis (reduced eGFR, hematuria, hypertension), and response to steroids. We considered each as tests to predict FSGS histology, compared proportions for the presence of the specific variable (chi-square), and calculated sensitivities and specificities.

Summary of Results A total of 178 patients were identified, 22 with FSGS, and 156 with MCD. There were no significant between-group differences in age, sex, or eGFR at the time of diagnosis. The FSGS group had a higher proportion of hypertension (40 vs 22%, p=0.09), hematuria (80 vs 47%, p=0.01), and nephritis (22 vs 1%, p=0.001) and was more likely to be steroid resistant after 6 weeks of treatment than the MCD group (67 vs 7%, p<0.001). As tests to predict FSGS, the presence of hematuria had a sensitivity of 0.80 (CI 0.56–0.93), and specificity 0.53 (CI 0.44–0.62), nephritis had a sensitivity of 0.22 (CI 0.07–0.48) and specificity of 0.99 (CI 0.95–0.99), and steroid resistance had a sensitivity of 0.67 (CI 0.43–0.85) and specificity 0.91 (CI 0.88–0.97). Combining steroid resistance with nephritis at diagnosis yielded a sensitivity of 0.80 (CI 0.56–0.93) and specificity 0.93 (CI 0.83–0.95). When we applied this combined indication for performing a kidney biopsy to our historical cohort, 58 (69%) fewer biopsies would have been performed.

Conclusions Clinical biomarkers at diagnosis combined with steroid response are accurate predictors of unfavorable NS in children. These objective indicators will be used in our newly developed clinical pathway to maximize the yield of

diagnostic FSGS biopsies while minimizing the number of unnecessary MCD biopsies.

346 TRYPTOPHAN PATHWAY ACTIVITY SPECIFIC TO ACUTE KIDNEY ALLOGRAFT REJECTION IN CHILDREN

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10.1136/jim-2016-000365.346

Purpose of Study Detection of rejection in pediatric kidney transplantation relies on kidney biopsy. Urinary metabolomics has shown potential for non-invasive diagnosis. We hypothesize that perturbations of the tryptophan (Trp) patheway may be detected in urine and associated with acute rejection.

Methods Used Urine samples from patients <19 years at transplant with concurrent surveillance or indication biopsies were assayed for Trp, serotonin (Ser) and kynurenine (Kyn) by mass spectrometry and normalized to creatinine (Cr). Samples were grouped based on Banff scoring of biopsy: T cell-mediated rejection (TCMR; n=33), borderline rejection (BRD; n=115), and NoTCMR (n=235). Univariate comparisons were performed between groups for the three metabolites metabolite ratios, with multivariable analysis to adjust for repeated measures.

Summary of Results Fifty-nine patients (mean age of 11.4 ±4.4 years) contributed 383 urine samples with a median of 6 (IQR 4–8) samples per patient. Univariate analyses showed significant differences between TCMR (0.009 ±0.006) and BRD (0.013±0.012) (p=0.007), and TCMR (0.009±0.006) and NoTCMR (0.013±0.010) (p=0.003) for Ser:Trp, and between TCMR (1.74±1.67) and NoTCMR (0.95±1.08) (p=0.011) for Kyn:Cr. Multivariate analysis of Ser:Trp (OR=0.476) differentiated TCMR (n=33) and pooled BRD and NoTCMR (n=350) AUC=0.89 (95%CI 0.84–0.94, p=0.034), while Kyn:Cr (OR=1.353) differentiated TCMR and pooled BRD and NoTCMR, AUC=0.91 (95%CI 0.88–0.95, p=0.02). Further analyses were performed to demonstrate independence of these two ratios from other potential indicators of rejection. The Kyn:Cr (OR=1.353, p=0.02) and Ser:Trp ratios (OR=0.475, p=0.034) discriminated for TCMR where deltaCr could not (OR=0.996 and 0.992 respectively). Presence of AMR increased odds of TCMR (OR=16.318) after adjusting for Kyn:Cr ratio (OR=1.356), which maintained discriminatory power (p=0.029). Presence of AMR also increased odds of TCMR (OR=15.27) after adjusting for Ser:Trp ratio (OR=0.551).

Conclusions Urinarytryptophan pathway metabolites are associated with TCMR. These findings support continued development of non-invasive, metabolomics-based diagnostics for allograft rejection.

347 PROSTATE CANCER METASTATIC TO THE RENAL ALLOGRAFT

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10.1136/jim-2016-000365.347

Case Report Malignancy is a recognized complication in allograft recipients and is increasing in incidence. This risk has been linked to the cumulative exposure to immunosuppression therapy, longer graft survival and the increasing age of transplant recipients. The risk of developing prostate cancer in male recipients of a renal allograft, once thought to be equal or less than that in the general population is now 2–5 fold higher. This perhaps is a result of the aging renal transplant population, and/or improved screening tests for prostate cancer. Regardless, these cancers are more aggressive than those occurring in the general population. However, the best management of these cancers has not been studied and treatment is similar to that given to the general population, with additional considerations for reducing immunosuppressants and conversion to sirolimus, an anti-proliferative immunosuppressant agent. We present a case of prostate cancer infiltrating a renal allograft in a patient previously diagnosed 2 years post-transplant with clinically localized de novo cancer. The patient initially opted to be treated with brachytherapy and a sirolimus based regimen in lieu of the calcinurin inhibitor. One year later, in the setting of a rising prostate specific antigen, androgen deprivation therapy was started. Five years after transplantation, our patient developed respiratory symptoms initially thought to be infectious in origin with some improvement after antibiotic treatment. Renal function remained normal with his baseline creatinine at 1.3 mg/dl. Eventually the diagnosis of sirolimus pneumonitis was made. Coincident with this, our patient developed severe renal transplant dysfunction requiring hemodialysis. A CT scan revealed pelvic adenopathy and a grossly abnormal appearing allograft that was new compared to a transplant ultrasound performed six months prior. A needle biopsy revealed high grade prostate cancer infiltrating the allograft. The patient opted to stop dialysis and passed peacefully. Prostate cancer rarely spreads to the kidney. This is the first report to our knowledge of prostate cancer invading the renal allograft. Heightened awareness of the increasing incidence of prostate cancer, the potential aggressiveness of the disease and unusual presentations in organ recipients is needed. Further studies regarding the management of such tumors are necessary.

Neuroscience II
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

348 MULTIMODAL BRAIN IMAGING IN PATIENTS RECEIVING BRIGHT LIGHT THERAPY FOLLOWING A MILD TRAUAMTIC BRAIN INJURY

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10.1136/jim-2016-000365.348

Purpose of Study Individuals who suffer an mTBI may develop post-concussion syndrome symptoms including issues with attention, mood, and sleep. Research shows that morning blue light exposure leads to regular entrainment of one's circadian rhythm, resulting in improved sleep

efficiency and daytime alertness. We hypothesized that morning blue light therapy (MBLT) will cause changes in the brain's function and structure that align with improved cognitive performance, mood, and sleep in patients recovering from an mTBI.

Methods Used Thirty-one participants with sleep disturbances following documented mTBI in the past 18 months were randomly assigned to the active treatment of MBLT (7M, 8F, mean age=23±7.5 years) or placebo condition of amber light therapy (ALT) (7M, 9F, mean age=23±7.1 years). Neurocognitive testing and brain magnetic resonance imaging were conducted at baseline and after 6 weeks of treatment.

Summary of Results In the MBLT group, voxel based morphometry showed increased gray matter volume in the left ($p<0.001$) and right pulvinar ($p=0.009$) between pre-and post treatment. Resting state functional connectivity demonstrated a positive significant correlation between the pulvinar and parietal area in the left (p-FDR=.003) and right (p-FDR<.001) hemispheres. Diffusion tensor imaging showed an increase in fractional anisotropy (FA) between the left parietal and pulvinar (2-sample t-test, $p=.063$). Cognitive performance analyses yielded a significant correlation between residual FA and residual Repeatable Battery for the Assessment of Neuropsychological Status total ($r=-.805$, $p=-.016$) and visuospatial constructive ($r=0.865$, $p=-.059$) scores. Mood analysis showed a correlation ($r=-.689$, $p=-.059$) between residual patient health questionnaire score, measuring depression, and residual FA. There were no significant correlations between brain changes and sleep data. ALT did not show significant brain changes or correlations with behavior.

Conclusions MBLT appears to promote structural and functional pathways within the visuospatial processing system after an mTBI. The improvement in the brain's functional and structural strength, mood, and neurocognitive performance suggests MBLT may be an effective non-pharmacological treatment for mTBI. The extent to which these changes are mediated by sleep remains to be determined.

349 THE RELATIONSHIP BETWEEN ABNORMAL WHITE MATTER CONNECTIONS AND WORKING MEMORY AND LANGUAGE ABILITY IN CHILDREN AT GENETIC RISK FOR SCHIZOPHRENIA

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10.1136/jim-2016-000365.349

Purpose of Study Schizophrenia (SZ) has been recognized as a neurodevelopmental disorder with characteristic language and memory deficits. Previous neuroimaging studies report decreased fractional anisotropy (FA), a measure of white matter (WM), in SZ. However, the timeline of WM abnormalities and their relationship to cognitive deficits is poorly understood. This study aims to utilize diffusion imaging and neurocognitive assessments to investigate the relationship between potential structural alterations in WM tracts associated with language and memory and cognitive scores in children at genetic high risk (GHR) for the disease.

Methods Used 3T diffusion-weighted images of children aged 7 to 12 (18 controls and 14 at GHR for SZ) were collected. Proprietary software was used to to create whole brain reconstructions of white matter tracts. Two anatomical tracts of interest were then extracted: a language tract, the arcuate fasciculus (AF), and a working memory tract, the superior longitudinal II fasciculus (SLF-ii). FA-t, a novel measure that enhances specificity for tissue by removing extracellular water, was obtained and compared between the GHR and control children. Correlations between scores on language and working memory tests will be completed with the FA-t values in the AF and SLF-ii, respectively.

Summary of Results Preliminary anlaysis of the FA-t demonstrates that there is a significant 16.6% decrease in FA-t in the right AF in GHR children under the age of 9 ($p<0.01$). These differences were not present in the right AF in GHR children between the ages of 10 and 12. Cognitive scores are collected but not available for analysis yet.

Conclusions Our findings of a reduction in FA-t in the right AF in children under 9 could suggest that early maturational alterations could be present in GHR children. FA has been shown to exhibit increases during this time, thought to reflect increased myelination. These changes may indicate a period of vulnerability. Correlations with performance on cognitive assessments may reveal a pathogenic mechanism for decreased scores.

350 THE EFFECTS OF RETINOIC ACID ON MUTANT ISOCITRATE DEHYDROGENASE GLIOMA CELLS

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10.1136/jim-2016-000365.350

Purpose of Study The majority of low grade gliomas and secondary glioblastomas carry a gain-of-function mutation in the gene isocitrate dehydrogenase (IDH1). Mutant IDH1 gliomas are phenotypically different from wild type IDH1 gliomas, including in chromatin remodeling and differentiation pattern. Retinoic acid (RA), a metabolite of vitamin A, is critical in cell differentiation in development and adult life, and has been used in treating hematological and other malignancies. In this study, we sought to understand the effects of RA on mutant IDH1 glioma cells in hopes to expand its therapeutic use to this glioma subtype.

Methods Used We used glioma cell lines TS667 (wtIDH1) and TS603 (muIDH1) to examine their proliferation rate in varying concentrations of RA (1 nM to 10 uM), measured at day 1, 3, 5, and 7. We studied transcriptomal changes in markers of stemness (*sox2, nestin*), differentiation (*tuj1, GFAP),* and apoptosis (*p21, p53*) between the wtIDH1 and muIDH1 after 3 and 6 days of 1 uM RA treatment via real-time PCR, and visualized these changes by immunofluorescence (IF) staining.

Summary of Results muIDH1 cells have a longer division time (>24 hours) than wtIDH1 cells (~14 hours). We observed a dose-dependent inhibitory effect of RA, with a

relative inhibition of ~50% at 1 uM RA compared to control group, in both cell lines. The gene expression profile of both cell lines at day 6 is similar to that of serum-treated differentiated cells. We observed a modest but significant decrease in *sox2*, a mild increase in *p53* and *p21*, and a dramatic increase in *GFAP*. IF studies support these findings. Lastly, with RA treatment both cell lines transform from homogeneous spheres to heterogeneous populations with various processes.

Conclusions muIDH1 cells exhibit a different biology from wtIDH1 cells, but the inhibitory effects of RA on both cell lines are similar. Our findings suggest RA pushes both muIDH1 and wtIDH1 cells into a differentiated, less proliferative state, and the inhibitory effects of RA in our growth curves may be a result of cells differentiating, rather than cell death. Our findings point to the possibility that survival benefit seen in patient clinical trials using RA may be a result of RA acting on the tumor microenvironment and/or immune cells, and not directly on the tumor cells themselves.

351 TUMOR NECROSIS FACTOR INCREASES EVOKED RESPONSE POTENTIAL IN CO-CULTURES OF NEURONS AND GLIA *IN VITRO*

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10.1136/jim-2016-000365.351

Purpose of Study There are profound connections between sleep and immune function, memory formation, and cognitive functioning. However, the precise mechanisms by which sleep is regulated are still unknown. TNF-α has been demonstrated to induce sleep when administered *in vivo*. Additionally, it has been shown to increase parameters associated with sleep, such as slow wave synchronization and slow wave power, *in vitro*. This experiment aims to further characterize the effects of TNF-α *in vitro* by examining the relationship between TNF-α and response potentials evoked from an imposed stimulus. Our hypothesis is that cells treated with TNF-α will have a greater magnitude of response to an imposed stimulus than cells that do not receive TNF-α treatment.

Methods Used Tissue was collected from the somatosensory cortex of wild type mouse pups (n=17), aged 0–3 days. Tissue was plated on a micro-electrode analyzer (MEA) and treated with a media that selected for neuron and glial growth. After two weeks of development, each culture was treated with either 0.1 ng of TNF-α, 0.01 ng of TNF-α, or isotonic saline. Following treatment, cultures were manually stimulated at a rate of 0.1 Hz for 30 minutes and response activity was measured and recorded. Data was analyzed to examine the average evoked response potential (ERP) within 500 ms of each manual stimulus. These ERPs were then averaged for the duration of the half hour experiment for each preparation.

Summary of Results The ERP showed a dose dependent response to treatment with TNF-α. Cells treated with the 0.01 ng preparation of TNF-α showed a 20% greater evoked response than saline controls. ERP in cells treated with 0.1 ng of TNF-α showed greater than a threefold increase when normalized against saline control, with an evoked response that was 341% of the ERP in control cultures.

Conclusions TNF-α is capable of modulating the activity of neuronal tissue *in vitro* in a manner that creates a more robust response to an imposed stimulus. Additionally, treatment with TNF-α demonstrates a response that is proportional to the dose applied. This suggests that TNF-α plays a dose dependent role in sleep homeostasis and the ability to fine tune evoked responsiveness at the cellular level.

352 A SIGNAL-TO-NOISE RATIO METRIC FOR COGNITIVE PERFORMANCE ON THE PSYCHOMOTOR VIGILANCE TEST

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10.1136/jim-2016-000365.352

Purpose of Study Fatigue from sleep loss degrades health, safety and cognition. The psychomotor vigilance test (PVT), which involves responding to visual stimuli at 2–10 s random intervals for 10 min, is a widely used, learning-curve-free, standardized assay of fatigue. However, there is no consensus on which metrics to extract from the PVT response times and what they say about the underlying cognition. Based on the diffusion model, which describes performance in terms of accumulation of evidence in central cognition, we developed a novel, signal-to-noise ratio (SNR) metric for the PVT to address this issue.

Methods Used The SNR was mathematically derived from the published one-boundary diffusion model for one-choice reaction time tasks and scaled logarithmically. The metric was applied to laboratory data from N=169 healthy individuals (ages 22–40, 85 females) subjected to 38 h of total sleep deprivation (n=99) or well-rested control (n=70). Subjects took the PVT at 2 h intervals while awake. Outcomes extracted were the SNR and two other, commonly used metrics: mean 1/RT (mean of reciprocal response times) and number of lapses of attention (response times≥500 ms). These were analyzed using mixed-effects ANOVA with fixed effects for condition, time awake and their interaction and a random effect on the intercept.

Summary of Results In accordance with the well-established homeostatic and circadian regulation of fatigue, the SNR reflected degradation of PVT performance across time awake modulated by time of day. The SNR exhibited similar levels of statistical significance (interaction $p<0.001$), sensitivity (large effect size, $f^2=0.38$) and robustness (ICC=0.47) as mean 1/RT and lapses of attention, and stood out by also accounting for the balance between cognitive processing speed and accuracy (i.e., speed-accuracy trade-off).

Conclusions By expressing performance in terms of the SNR, the PVT may be used as a generic probe of the fidelity of cognitive processing. The SNR metric thus provides a framework for extending the interpretation of PVT performance to include other cognitive domains beyond vigilance. As such, this novel metric may help to

resolve the debate regarding what PVT performance reveals about cognitive functioning.

353 EYE MUSCLE SPASMS CO-ACTIVATE WITH CEREBELLAR AND SENSORIMOTOR CORTICAL REGIONS IN BLEPHAROSPASM

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10.1136/jim-2016-000365.353

Purpose of Study Blepharospasm (BSP) is a focal dystonia characterized by uncontrolled orbicularis oculi contractions. Previously thought to be a purely motor disorder of the basal ganglia, dystonia is now viewed as a network disorder with evidence of widespread brain dysfunction. However, it is unclear what regions play key roles in BSP.

Methods Used Functional MRI (fMRI) data were collected on 15 patients with BSP (4M:11F; mean age 62.2 ±8.0; disease duration 8.4±7.3 y) during an 8-minute resting state with eyes open. Orbicularis oculi contractions were recorded by MRI-compatible surface electromyography (EMG). Spasm severity was modeled using amplitude of EMG signal (EMG-Amp) and included in multiple regression fMRI analysis using SPM8. Primary outcome was within BSP group blood-oxygen-level dependent (BOLD) activations that co-varied with EMG-Amp (individual voxel-level threshold $p \leq 0.005$; cluster size threshold 50 voxels). Secondary analyses included Spearman's rank correlation testing ($p < 0.01$) of imaging findings with BSP duration/severity by Unified Dystonia Rating Scale (UDRS), Jankovic Rating Scale (JRS), Burke-Fahn-Marsden Scale (BFM), and Global Dystonia Rating Scale (GRS).

Summary of Results fMRI data were excluded for one subject due to excessive movement during scanning. EMG-Amp co-activated with bilateral sensorimotor regions of the cerebellum (lobule 6) and postcentral gyri (Table 1). Activity in the postcentral gyri negatively correlated with disease severity: UDRS (R/L:R^2=0.60, R^2=0.48), BFM (R/L:R^2=0.74, R^2=0.71) and GRS (R/L:R^2=0.66, R^2=0.67). BFM negatively correlated with left cerebellar activity (R^2=0.37). Disease duration did not correlate with fMRI.

Conclusions Co-activation of postcentral gyri and cerebellum is consistent with known sensory and motor dysfunction in BSP and substantiates the network disorder model. Negative correlation of disease severity with sensorimotor activation may indicate that greater network impairment manifests as increased BSP symptom severity.

Abstract 353 Table 1 Brain areas with significant clusters of co-activation with EMG-Amp

Side	Region	Cluster size (mm3)	MNI coordinates X	Y	Z	Peak t value
R/L	Cerebellum lobule 6	126	–12	–63	–27	6.09
R	Postcentral gyrus	56	63	–9	18	6.11
L	Postcentral gyrus	56	–60	–15	12	5.18

354 INTERACTION BETWEEN THE BASAL GANGLIA AND THE CEREBELLAR CIRCUITS IN PARKINSONIAN RESTING TREMOR

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10.1136/jim-2016-000365.354

Purpose of Study Parkinson disease (PD) is characterized by the depletion of dopamine in the basal ganglia. However, dysmodulation of the motor system by the basal ganglia alone can not account for resting tremor, a prominent symptom of the disease. Recent studies have indicated the role of the cerebellar circuit and its interaction with the basal ganglia in the pathophysiology of resting tremor. The purpose of this study is to determine the distinct contribution of the basal ganglia and the cerebellar circuits in generating resting tremor.

Methods Used Concurrent EMG and BOLD fMRI data were collected from 24 PD patients in resting state. Data analysis was performed to determine the brain activity covarying with the tremor. The EMG waveform was processed to extract tremor amplitude at its peak frequency. To investigate the dynamic properties of the tremor (i.e. how it is switched on and off), temporal derivative of EMG data was calculated to represent tremor onset and offset. Tremor amplitude and tremor onset/offset were then correlated with fMRI signal using general linear model.

Summary of Results Preliminary analysis on single subject data shows the results below. With tremor amplitude, brain activation is seen predominantly in the contralateral motor cortex and thalamus, and ipsilateral cerebellum, but not in any part of the basal ganglia. Similar pattern of activation of the motor cortex, thalamus, and cerebellum is seen with tremor onset/offset. However, tremor onset/offset is also correlated with activation of the globus pallidus (part of the basal ganglia).

Conclusions Activation of the cerebellum, correlated with both tremor amplitude and tremor onset/offset, indicates the involvement of the cerebellar circuit in the pathophysiology of resting tremor. The activation of the pallidal part of the basal ganglia is associated with tremor onset/offset but not with tremor amplitude, suggesting the basal ganglia plays a role in initiating tremor, but not in driving it. This result is in agreement with a single prior study, confirming that our methods of data analysis were robust. Further analysis at the population level will be done to strengthen this finding.

355 DISTINGUISHING GLIOBLASTOMA RECURRENCE FROM PSEUDOPROGRESSION WITH MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY

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10.1136/jim-2016-000365.355

Purpose of Study Glioblastoma multiform (GBM) is the most common malignant brain cancer with a 3.3% 2-year survival rate. The current standard of care—resection followed by radiotherapy (RT) and concurrent temozolomide

(TMZ) chemotherapy—causes inflammation called pseudoprogression (PsP), which appears as abnormal MRI signals resolving in 2–6 months. Other imaging methods like DTI, PET, and SPECT have failed to differentiate PsP. Using superparamagnetic iron oxide nanoparticles (SPION) and specific metabolic signatures, we hope to determine whether T2 MRI and MRS can characterize GBM growth or PsP.

Methods Used *In vitro*—We cultured two glioma cell lines and tested cell survival after TMZ treatments with the sulforhodamine B (SRB) and trypan blue exclusion (TBE) assays, and after RT using clonogenic assays. We used MRS to evaluate metabolic changes after treatment.

In vivo - We injected U251 cells into the right flanks of nude mice and intracranially into another cohort. Once the tumors have grown, we will perform pre-treatment MRI with SPION, tumor blood volume, and FDG-PET for the flank model. We will treat the mice with oral TMZ for 5 days, with concurrent RT on the first day. We will repeat the MRI and PET imaging and then harvest tissue for macrophage flow cytometry and IHC/Prussian blue staining. We will repeat this study with GL261 cells in a cohort of wild type mice.

Summary of Results GBM survival declined linearly with TMZ on TBE assays. SRB assays were inconsistent due to post treatment cell clumping. GBM survival declined exponentially after RT on clonogenic assays. Lactic acid production decreased with TMZ and RT. Glucose uptake decreased with RT but did not change with TMZ.

Pre treatment scans should show no SPION T2 signal reduction. If macrophages take up iron and tumor cells do not, we expect SPION T2 signal reduction with PsP but not tumor growth. Macrophages after treatment on cytometry will confirm PsP, and iron should colocalize with macrophages but not tumor cells on histology.

Conclusions GBM cells are slightly resistant to RT in vitro. The greater metabolic effect of RT suggests they are more susceptible to RT than TMZ. If our results with the in vivo study are as expected, we can conclude that SPION contrast in MRI imaging can distinguish PsP from tumor progression non-invasively for GBM.

Surgery IV
Concurrent Session
10:15 AM – 12:30 PM
Friday, January 27, 2017

356 CANCELLED

357 INTRAVENOUS LIDOCAINE REDUCES POST-OPERATIVE PAIN AND OPIATE REQUIREMENT IN PATIENTS UNDERGOING EXTERNAL FIXATION

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10.1136/jim-2016-000365.357

Purpose of Study In external fixation for limb reconstruction, adequate analgesia must be balanced with timely mobilization and discharge. At BC children's hospital, a standardized multimodal anaesthesia regimen was developed that includes acetaminophen, pregabalin, dexmedetomidine, opioids and IV lidocaine infusion and used for last two years in external fixation.

Methods Used We conducted a retrospective chart review of all children who have undergone external fixation between Sept 2014 and Dec 2015. We recorded pain scores in PACU and in ward, amount of opiate consumed, and duration that the patient was on continuous opioid infusion (COI).

Summary of Results Twenty-five children had undergone limb reconstruction with external fixation during the study time period. 13 patients were given standardized regimen with intraoperative lidocaine infusion, and 12 were given a regimen without lidocain infusion. We elected to look only at tibial frames. Patients with multilevel frames, footframes, and multiple frames were excluded from the analysis since those were incompatible for comparing the postoperative pain with a standard tibial frame.

The variables included in the analysis were: peak and first PACU pain scores, amount of opioid consumed while on COI, and duration of COI. Student's t-test was conducted to compare whether there was statistically significant difference between the two groups.

The patients in lidocaine group (N=9) consumed lower total amounts of morphine equivalent per kg of body mass while on COI than those in the non-lidocaine infusion group (N=10) (967 mg/kg vs 1595 mg/kg; p=0.044). The durations of COI was shorter for the lidocaine group over those in non-lidocaine group, though not statistically significant, there was clinically significant decrease in 10 hours of COI (3022 min vs 3601 min; p=0.106). The lidocaine group had clinicially significant reduction of peak PACU pain, though this was not statistically significant (2.78 vs 5.1; p=0.068).

Conclusions Preliminary results indicate lower pain score in PACU, lower opioid infusion consumption, shorter duration of COI, and reduction in the post-operative opioid infusion amount. Lidocaine infusion may aid in pain management in limb reconstruction using an external fixator device.

358 RELATIONSHIP OF PERIOPERATIVE VARIABLES AND RENAL FUNCTION IN PEDIATRIC RENAL TRANSPLANTATION: A SINGLE-CENTER STUDY

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10.1136/jim-2016-000365.358

Purpose of Study In the pediatric population, there are a variety of kidney conditions, which can lead to chronic kidney disease. Kidney transplantation is the current gold standard treatment for chronic kidney disease and kidney failure, however, kidney rejections remains a major concern when evaluating the outcomes of kidney transplantation. Certain patient and donor variables, such as demographics, etiology, donor source, recipient's age at transplantation,

and HLA-matching, have had their relationships with renal graft outcome (RGO) well described by researchers. Perioperative factors such as intraoperative hemodynamic factors, have yet to have their effects on RGO investigated. This study aims to present the largest data set of pediatric renal transplantation from a single centre to-date, and to examine the impact of perioperative variables on RGO.

Methods Used A single-center retrospective cohort study was conducted at a tertiary care service facility, British Columbia's Children's Hospital in Vancouver, Canada. The study included all patients <19 years of age who had their first renal transplantation between January 1st, 1992, and May 31st, 2013. There were a total of 139 participants. The sample was divided into 3 age groups: <6, 6–12, >12, year-old (yo). Some of the perioperative factors compared across age groups included: pre-operative blood pressures and BMI, weight-normalized volume of intraoperative blood products used, and central venous pressure during the participants' stay in the intensive care unit postoperatively.

Summary of Results Patients less than 6 years of age at transplantation received a significantly greater weight-normalized total amount of blood products compared to those greater than 12 years of age (20 cc/kg vs 8 cc/kg, p=0.0312). Patients who were older than 12 years at transplantation had significantly lower z-scores of their lowest intraoperative systolic and diastolic blood pressures than the other two age groups: <6 yo (p=0.0029, p=0.0015, respectively) and 6–12 yr (p=0.0017, p=0.0204, accordingly).

Conclusions Perioperative factors including blood pressure and volume are significantly different in various age groups of renal transplantation.

359 CONSIDERATION OF LIMB LENGTH INEQUALITY IN THE TREATMENT OF UPPER EXTREMITY PEDIATRIC BONE SARCOMA

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10.1136/jim-2016-000365.359

Purpose of Study Reporting on treatment of pediatric upper extremity bone sarcomas remains limited. Because of the rarity of the disease, cases of upper extremity origin have historically been combined with lower extremity origin. However, combination does not allow opportunity to differentiate unique surgical and functional outcomes for the upper extremities. Specifically, a need exists to delineate whether or not limb length inequality present clinical and functional deficits in the upper extremity.

Methods Used We retrospectively reviewed the records of 15 patients treated or followed at Children's Hospital Colorado after surgical treatment and/or radiation therapy for sarcoma of the scapula, humerus, or clavicle between 2003 and 2014. Demographics, histologic diagnosis, surgical procedure, tumor margins, chemotherapy and radiation, complications, follow up, and survival outcomes were collected.

Summary of Results Location of sarcoma included eight proximal, one distal, and two total humerus, three scapula, and one clavicle. With chemotherapy, 11 patients had surgery, three surgery and radiation, and one with only radiation. Of the few complications that arose, most were due to nonunion of graft host junctions and shoulder instability. Desire for limb length equality resulted in multiple surgeries mostly due to instability. No additional treatment with presence of limb length inequality led to fewer complications.

Conclusions Epiphyseal damage and growth loss complicated by shoulder instability occurs with radiation therapy and humeral resection. The instability worsens with additional forces generated through limb lengthening procedures leading to decreased function and further operations. While cosmetically different, a short humerus in many of these patients with weak abduction of the arm is advantageous as it brings the elbow proximally for daily living function like moving the hand to the mouth. Although significant skeletal growth remains in many of these patients, detailed examination of upper extremity cases alone in this study concludes that limb length inequality in the upper extremity is a cosmetic problem only and not an indication for surgery.

360 OPTIMAL TIMING OF RADIATION IN IMPLANT BASED BREAST RECONSTRUCTION

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10.1136/jim-2016-000365.360

Purpose of Study Implant based reconstruction constitutes approximately 80% of breast reconstructions performed in the United States. Many of these patients have immediate reconstruction and ultimately undergo radiotherapy. Among these patients, there are two groups: 1. those that have the permanent implant in place prior to radiotherapy (direct-to-implant reconstruction, tissue expander reconstruction with permanent implant exchange prior to radiotherapy) (Implant group), and 2. those that have tissue expander (TE) reconstruction followed by radiotherapy, and then implant exchange (TE group). The purpose of this study was to retrospectively compare the outcomes among these groups of patients treated at Loma Linda University between 2012 and 2015.

Methods Used The primary endpoint was the rate of reconstruction failure, defined as implant removal and/or change to a flap based technique. Secondary endpoints were the rates of major (requiring readmission or surgery) and minor complications.

Summary of Results There were 10 patients in the Implant group and 28 patients in the TE group. Patient characteristics were similar in both groups except the TE group had higher average BMI (28 vs 25, p=0.0181) and a higher incidence of hypertension (10/28 vs 0/10, p=0.0377). The failure rate was 0/10 (0%) in the Implant group compared to 11/28 (39%) in the TE group (p=0.0372). In the Implant group, 2/10 patients (20%) had major complications, compared to 16/28 patients (57%) in the TE group (p=0.0673).

Conclusions When adjuvant radiation therapy is needed in implant based reconstruction, completing reconstruction prior to radiation therapy appears to have a higher success rate and may result in fewer major complications when compared to completing reconstruction after radiation therapy. Further study is warranted.

361 THE SEARCH FOR A NOVEL HUMAN SKIN STERILANT

Lewis M, Wong AL, Schaeffer BZ, Bauer B, Botimer G. *Loma Linda University, Loma Linda, CA.*

10.1136/jim-2016-000365.361

Purpose of Study Post operative infection causes major problems, especially following total joint implant surgery. Bacteria, including *P. acnes*, residing on and in the human skin at the site of surgical incision have been considered a source of post operative infections, especially in shoulder surgery. The purpose of this study was to determine the sterilant effect of a new broad spectrum antibiotic, protocatechuic acid.

Methods Used We performed three randomized trials involving 45 medical students. Trial I used chloroprep, betadine, and 1% PCA in sterile water as reagents. Trial II used 10% PCA in 70% isopropyl alcohol and a control of 70% isopropyl alcohol. Trial III used 17% PCA (20 g PCA, 85 ml 70% isopropyl alcohol, 15 ml propylene glycol and 5 ml of essence of peppermint oil) and 70% isopropyl alcohol. Pre and post skin culture harvesting techniques were standardized for all three trials and examined for exact bacterial species by DNA sequencing and or biochemical analysis. Pre and post culture colony growth were compared between the test reagents and controls.

Summary of Results Trial I – All the post-test chloroprep cultures had no growth. 1% PCA reduced to no growth in 7/16 aerobic and 4/6 anaerobic, reduced growth in 8/16 aerobic, and had 1/16 aerobic with no growth in pre and post-test cultures. Betadine showed no growth in 6/11 aerobic and 7/11 anaerobic post-test cultures.

Trial II – 10% PCA showed no growth in 10/11 aerobic and 9/11 anaerobic post-test cultures. 70% isopropyl alcohol showed reduced growth in 6/11 aerobic and 4/11 anaerobic post-test cultures.

Trial III – 17% PCA showed no growth in 10/12 aerobic and 11/12 anaerobic post-test cultures. 70% isopropyl alcohol showed no growth in 10/12 aerobic and 9/12 anaerobic post-test cultures.

Conclusions This study showed that concentrations of PCA greater than 10% were better than 70% isopropyl alcohol alone and betadine, but inferior to chloroprep at reducing post-test cultures to no growth. Concentrations greater than 10% PCA were shown to eliminate common pathogens. The addition of the skin penetration enhancers (propylene glycol and essence of peppermint oil) minimally improved the results.

362 CANCELLED

363 PREOPERATIVE CAPTURE OF AMERICAN SOCIETY OF ANESTHESIOLOGY CLASS AND FUNCTIONAL HEALTH STATUS FOR THE SURGICAL RISK PREOPERATIVE ASSESSMENT SYSTEM

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10.1136/jim-2016-000365.363

Purpose of Study This study seeks to develop novel methods for preoperative capture of American Society of Anesthesiology Physical Status Classification (ASA Class) and American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Functional Health Status (FHS) allowing use in the Surgical Risk Preoperative Assessment System (SURPAS). SURPAS is a surgical risk prediction system that utilizes 7 preoperative variables (including FHS and ASA) to predict risk of 9 clinically meaningful postoperative outcome clusters. ASA Class is a metric that assesses the health status of patients prior to surgery while FHS is a metric that assesses the independence of patients in engaging in activities of daily living prior to surgery. ASA class and FHS are not routinely assigned by surgeons in the preoperative clinic visit limiting their use with SURPAS, further limiting the system's utility for guiding patient/provider decision making, informed consent, and perioperative interventions. This study seeks to determine if surgeons can be trained to consistently assign ASA class and FHS with a high degree of concordance with anesthesiologists and ACS NSQIP surgical clinical reviewers who traditionally assign these scores as an important step to bringing SURPAS into clinical use.

Methods Used Because ASA class and FHS have been shown to have high inter-provider variability focus groups with anesthesiologists and ACS NSQIP surgical clinical reviewers will be held to determine intangible factors considered when determining ASA class and FHS. This will guide production of a 1-page classification guide for surgical clinic staff to use when determining ASA class and FHS. Patient cases from the ACS NSQIP dataset representative of a variety of ASA class and FHS determinations will be assigned a consensus ASA class and FHS by anesthesiologists and surgical clinical reviewers respectively. Participating surgeons will then be shown the clinic note of the selected patients and asked to determine ASA class and FHS. ASA class and FHS determinations made by surgeons will be compared to consensus scores evaluating concordance.

Summary of Results This study is on-going and will report results at the WMRC.

Conclusions This study is on-going and will report conclusions at the WMRC.

364 TREATING MACULAR DEGENERATION WITH POLYACRYLONITRILE FIBERS

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10.1136/jim-2016-000365.364

Purpose of Study Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. There are two forms of the disease: non-exudative (dry) and exudative (wet). The wet form accounts for 10% of AMD and is characterized by choroidal neovascularization. 10–50% of the dry form, characterized by lipoprotein deposits that cause atrophy to the retinal pigment epithelium, can develop into wet form. The pathogenes is unclear, and thus treatment options are limited. The alternative complement pathway has been implicated to play a role, in particular complement factor D (CFD). The

purpose of this study is to determine if polyacrylonitrile (PAN) membranes capable of adsorbing CFD are biocompatible to see if it has a role in treating and preventing dry AMD. We will also run protein sequestration studies to determine the efficacy of PAN fibers adsorbing other proteins implicated in dry AMD.

Methods Used Wild-type Brown Norway Rats and wild-type New Zealand White Rabbits will be used in this model. A 4 mm segment of PAN fiber will be injected into the vitreous cavity of one eye, while the other eye will be used as control. An electroretinogram (ERG) will be performed before the injections and 45 days after injections to determine whether retinal toxicity is present. The eyes will also be used for histology to look at retinal cell counts and signs of inflammation. In order to test protein sequestration, we will incubate the proteins implemented in dry AMD with PAN fibers to determine protein concentration reduction using spectrometry. We will also run experiments to visualize adsorption of protein onto PAN fibers using fluorophores.

Summary of Results We expect to see no significant change in latency and amplitude comparing our treatment ERG to the control ERG. We expect the control eye and treatment eye to look similar on histology with no signs of inflammation or decreased retinal cell count in comparison. Our protein sequestration studies so far have shown that PAN fibers can adsorb many proteins implicated in dry AMD, including CFD, C1q, C3, C3a, C5, C5a.

Conclusions We hope to conclude that PAN fibers are biocompatible in the eye and that they can adsorb proteins associated with dry AMD. Future directions would include intraocular injections of the PAN fibers in a dry AMD animal model.

JOINT PLENARY SESSION WAFMR, WSCI, WAP AND WSPR 1:30 PM – 5:00 PM Friday, January 27, 2017

365 FORMER PRETERM LAMBS HAVE NEURODEVELOPMENTAL IMPAIRMENTS LATER IN LIFE

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10.1136/jim-2016-000365.365

Purpose of Study Neurodevelopmental impairment (NDI) is often a long-term problem for survivors of premature birth. NDI increases with prolonged mechanical ventilator (MV) support. Preterm lambs that are supported by MV also develop diffuse damage to brain white and gray matter, and the hippocampus. We hypothesized that former preterm lambs (FPT) supported by MV will have NDI later in life.

Methods Used Fetal lambs delivered at 128–130 d (term~150 d) were supported by MV for 3 d (n=6, m:f 3:3) before being weaned from respiratory support. The FPT lambs lived for 6 months (M; 5 M corrected postnatal age, cPNA). Control lambs (n=14, m:f 5:9), born at term, lived 5 M. FPT were habituated to the test room. Tests were 1) novel objects, 2) mirror, and 3) maze, and were done on sequential days. Tests were repeated as trials of 10-min each, with a 30-min rest period between trials. The novel object test had four 10-min trials, with different novel objects/trial. The mirror test had two 10-min trials. The maze test was repeated on 3 sequential days; days 1 and 2 each had two 10-min trials, whereas day 3 had four 10-min trials. For the novel object and mirror (reflective vs non-reflective surfaces) tests, time to first encounter with an object, number of encounters with an object, and total time spent with an object were recorded. For the maze test, time to locate the reward (bottle of milk) was recorded. Repeated testing was done at 5 M (cPNA for FPT).

Summary of Results Summary results are presented because of small sample size (6) for FPT lambs. Compared to control term lambs, FPT lambs tested at 2 M cPNA (weaning from milk) and 5 M cPNA (equivalent to ~6 y for humans) 1) spent more time with the first novel objects encountered than with novel objects as they were subsequently presented, 2) spent equal time with the non-reflective surface relative to the mirror, and 3) took almost twice the time to find the maze reward.

Conclusions Our results suggest that FPT lambs are less inquisitive and slower to complete a rewarded task compared to control term lambs. These initial results suggest that 3 d of MV of preterm lambs is sufficient to cause NDI that persists later in life. (HL110002, HL062875; Division of Neonatology)

366 A PATIENT-CENTERED STUDY OF THE DIAGNOSIS AND CLINICAL CHARACTERISTICS OF JOUBERT SYNDROME

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10.1136/jim-2016-000365.366

Purpose of Study Joubert syndrome is a rare multisystem genetic disorder with a characteristic posterior fossa brain malformation. Information regarding the clinical course is limited, and clinical guidelines are lacking. We sought to identify early diagnostic features and characterize the clinical manifestations of Joubert syndrome as reported by affected families.

Methods Used Using the crowd-sourcing platform *Mosaic*, families proposed research topics and researchers, providers and caregivers collaborated to define study aims based on response commonalities. Data points for extraction were decided upon and included method of diagnosis, and early (first year of life) and general clinical and behavioral symptoms. Parent reported retrospective data were then obtained from 288 participants (median age at collection 6.4 years) in the *Joubert Syndrome and Related Disorders Foundation* patient database.

Summary of Results Mean age at diagnosis was 33 months (range 0–18 years). The majority of diagnoses were

made via a combination of MRI findings and clinical features, while genetic testing was a component of diagnosis in just 12.5%. Only 5 had a prenatal diagnosis. The most common early symptoms included breathing issues (64%), kidney problems (18%), and retinal abnormalities (10%). Liver problems and seizures were rarely reported before one year. The most common symptoms overall were low tone (93%), eye problems (85%), sensory (76%) and behavioral (55%) issues and abnormal breathing (55%). Communication issues were reported in 78%, of whom 36% were non-verbal. The median age of sitting and walking was 13–16 months and 3 years respectively.

Conclusions Our study provides valuable patient-centered insight into the diagnostic, clinical and behavioral characteristics of Joubert syndrome. Educational initiatives focused on early symptoms and characteristic signs on prenatal imaging, combined with increased utilization of genetic testing may facilitate earlier diagnosis and intervention while minimizing parental anxiety and overall cost.

367 SURVIVAL IN *BRCA1* OR *RAD51C* METHYLATED VERSUS MUTATED OVARIAN CARCINOMA

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10.1136/jim-2016-000365.367

Purpose of Study In ovarian carcinoma, mutations in genes in the homologous recombination DNA repair (HRR) pathway, including *BRCA1* and *RAD51C*, are associated with increased survival and specific clinicopathologic features. Promoter hypermethylation is an alternate mechanism of reducing gene expression. We evaluated whether methylation of *BRCA1* and *RAD51C* is also associated with improvement in survival and with similar clinicopathologic phenotypes.

Methods Used 332 primary ovarian carcinomas were assessed for promoter methylation of *BRCA1* and *RAD51C* using methylation-sensitive PCR and for damaging germline and somatic mutations in 16 genes associated with HRR: *ATM, ATR, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, MRE11A, NBN, PALB2, RAD51C, RAD51D, RBBP8, SLX4,* and *XRCC2*.

Summary of Results *BRCA1* methylation was detected in 22 (6.6%) and *RAD51C* methylation in 9 carcinomas (2.7%). Germline or somatic mutations in one or more HRR genes were found in 95 carcinomas (29%). Mutation and methylation of *BRCA1* and *RAD51C* were mutually exclusive (P=0.0013). Women with *BRCA1* methylation (57.7 years±2.5) or *BRCA1* mutations (mean 54.1 years ±1.4) were younger than those without methylation or mutations (63.3 years±0.8; P=0.0293, P<0.0001). *BRCA1* methylation and germline *BRCA1* mutation were both associated with high grade serous histology (P=0.0453, P=0.0010) and *TP53* mutation (P=0.012, P=0.0037). *BRCA1* mutation was associated with increased sensitivity to platinum chemotherapy (P=0.03) while *BRCA1* methylation was not. Unlike HRR mutations, methylation was not associated with improved overall survival compared to not mutated not methylated cases. Median overall survival was 41 months in methylated, 43 months in neither mutated nor methylated, and 63 months in mutated cases.

Conclusions Patients with *BRCA1* methylation share some clinical characteristics with patients with germline or somatic *BRCA1* mutations including younger age, predominantly high grade serous histology, and frequent *TP53* mutations. However, *RAD51C* or *BRCA1* methylation is not associated with improved survival or increased sensitivity to platinum chemotherapy as is seen with mutation of these genes. Possibly, methylation is more readily reversed than mutation, allowing more rapid development of platinum resistance and negating any impact on overall survival.

368 MEASURING UNMET NEEDS FOR ANTICIPATORY GUIDANCE AMONG ADOLESCENTS AT SCHOOL-BASED HEALTH CENTERS

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10.1136/jim-2016-000365.368

Purpose of Study Our previously validated Youth Engagement with Health Services (YEHS!) survey measures adolescent health care quality. The survey response format allows adolescents to indicate whether their needs for anticipatory guidance were met. Here, we describe the unmet needs for anticipatory guidance reported by adolescents and identify adolescent characteristics related to unmet needs for guidance.

Methods Used We administered the survey in 2013–2014 to 540 adolescents who used school-based health centers in Colorado and New Mexico. A participant was considered to have unmet needs for anticipatory guidance if they indicated that guidance was needed on a given topic but not received, or guidance was received that did not meet their needs. We calculated proportions of students with unmet needs for guidance. We examined associations between unmet needs for guidance and participant characteristics using chi-square and logistic regression.

Summary of Results Among participants, 47.4% reported at least one unmet need for guidance from a health care provider in the past year. Topics with the highest proportions of adolescents reporting unmet needs included healthy diet, stress, and body image. In logistic regression modeling, adolescents at-risk for depression and those with minority or immigrant status had increased unmet needs for guidance. Adolescents reporting receipt of patient-centered care were less likely to report unmet needs for guidance.

Conclusions The YEHS! survey provides a needs-based measurement of anticipatory guidance received that may support targeted improvements in the delivery of adolescent preventive counseling. Interventions to improve patient-centered care and preventive counseling for vulnerable youth populations may be warranted.